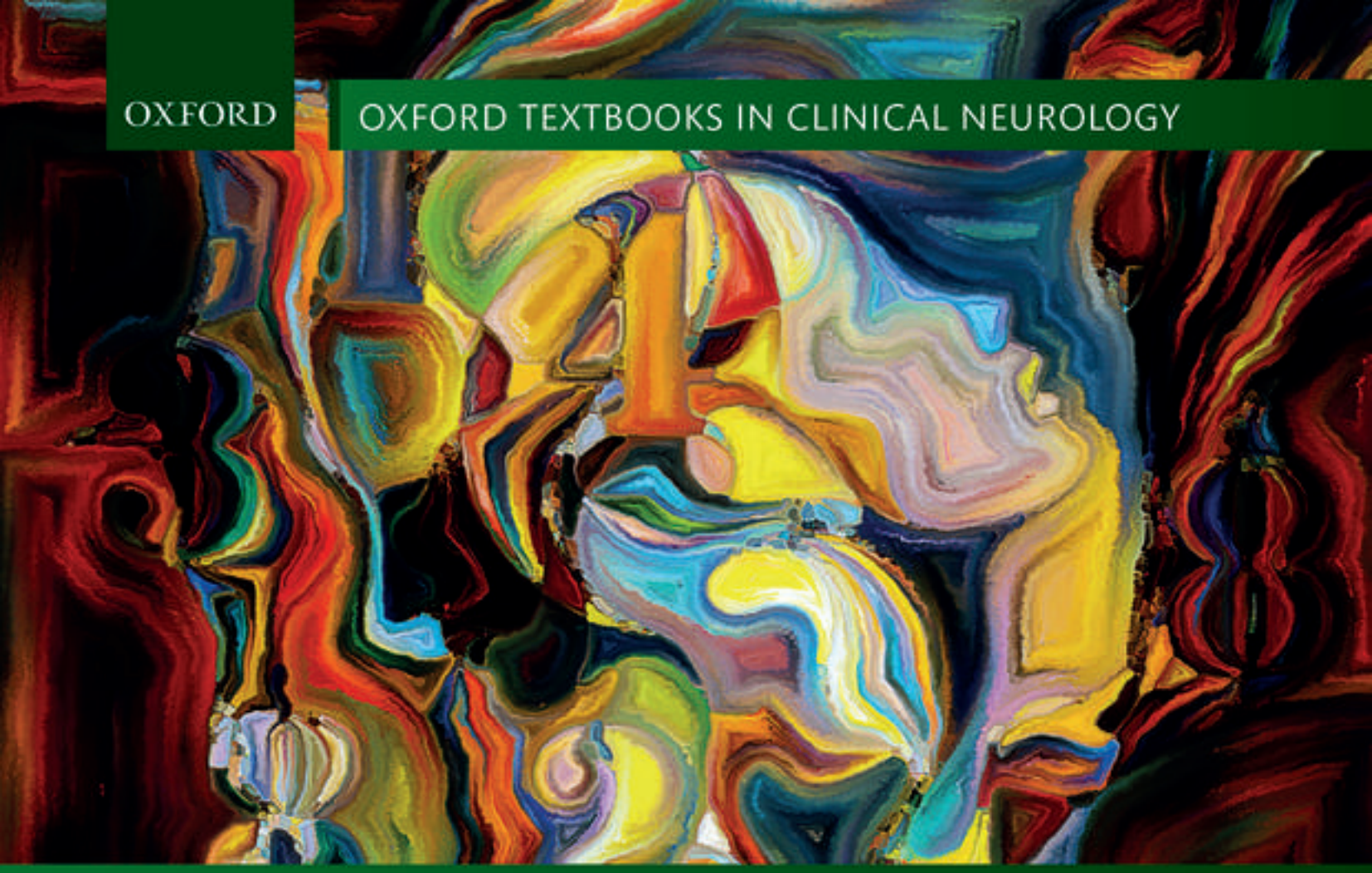

OXFORD TEXTBOOKS IN CLINICAL NEUROLOGY

Oxford Textbook of Headache Syndromes

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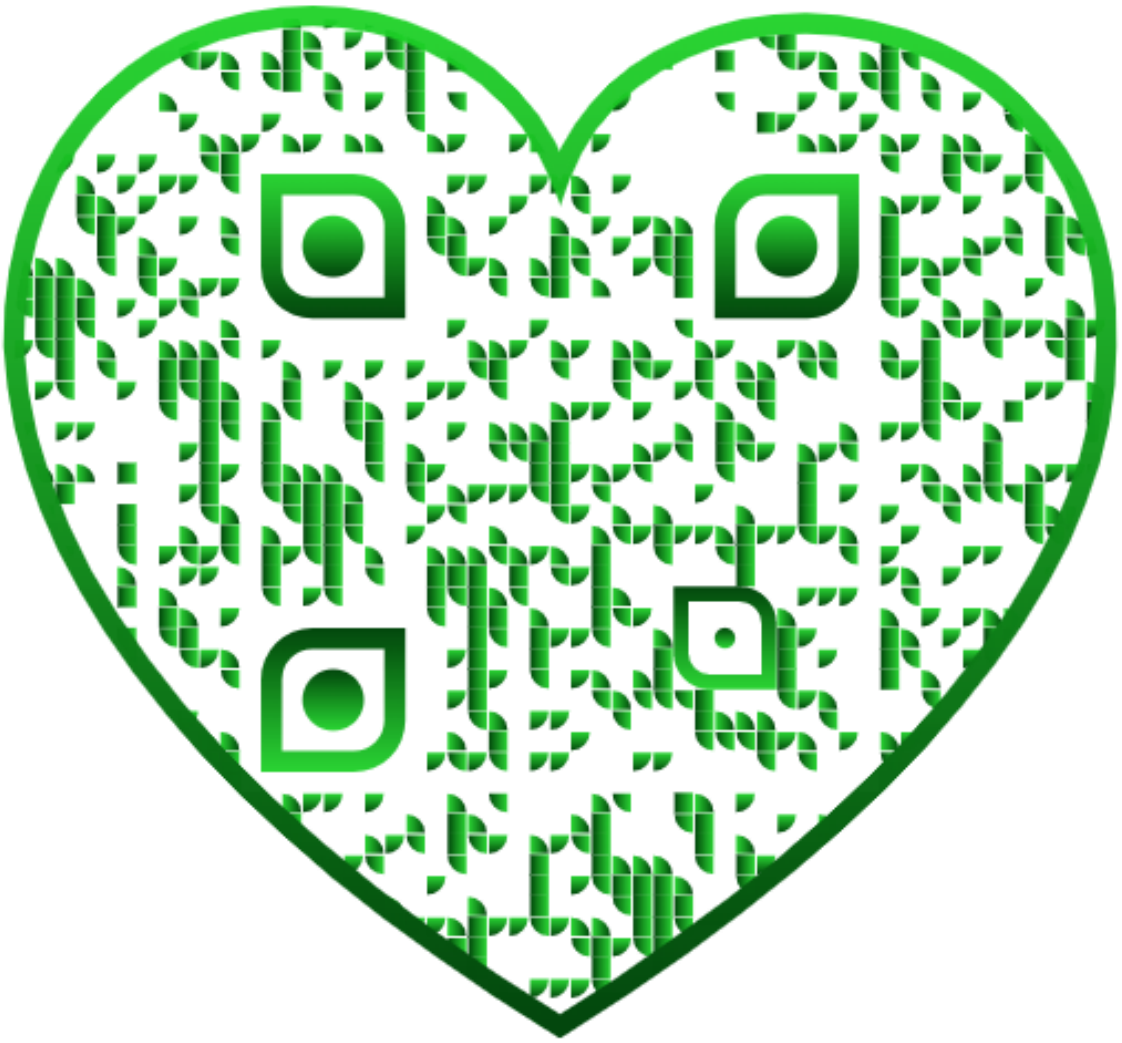

Oxford Textbook of

Headache Syndromes

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Contents

Abbreviations ix
Contributors xiii

PART 1
General introduction

1. **Classification and diagnosis of headache disorders** 3
   Jes Olesen and Richard B. Lipton
2. **Taking a headache history: tips and tricks** 12
   James W. Lance and David W. Dodick
3. **Diagnostic neuroimaging in migraine** 17
   Mark C. Kruit and Arne May
4. **Headache mechanisms** 34
   Andrew Charles
5. **Headache in history** 45
   Mervyn J. Eadie

PART 2
Migraine

6. **Migraine: clinical features and diagnosis** 61
   Richard Peatfield and Fumihiko Sakai
7. **Migraine trigger factors: facts and myths** 67
   Guus G. Schoonman, Henrik Winther Schytz, and Messoud Ashina
8. **Hemiplegic migraine and other monogenic migraine subtypes and syndromes** 75
   Nadine Pelzer, Tobias Freilinger, and Gisela M. Terwindt
9. **Retinal migraine** 92
   Brian M. Grosberg and C. Mark Sollars
10. **Migraine, stroke, and the heart** 98
    Simona Sacco and Antonio Carolei
11. **Non-vascular comorbidities and complications** 110
    Mark A. Louter, Ann I. Scher, and Gisela M. Terwindt
12. **Migraine and epilepsy** 120
    Pasquale Parisi, Dorothée Kasteleijn-Nolst Trenité, Johannes A. Carpay, Laura Papetti, and Maria Chiara Paolino
13. **Migraine and vertigo** 128
    Yoon-Hee Cha
14. **Treatment and management of migraine: acute** 138
    Miguel J. A. Láinez and Veselina T. Grozeva
15. **Treatment and management of migraine: preventive** 152
    Andrew Charles and Stefan Evers
16. **Treatment and management: non-pharmacological, including neuromodulation** 165
    Delphine Magis

PART 3
Trigeminal autonomic cephalgias

17. **Classification, diagnostic criteria, and epidemiology** 177
    Thijs H. Dirkx and Peter J. Koehler
18. **Cluster headache: clinical features and management** 182
    Ilse F. de Coo, Leopoldine A. Wilbrink, and Joost Haan
19. **Paroxysmal hemicrania: clinical features and management** 190
    Gennaro Bussone and Elisabetta Cittadini
20. **SUNCT/SUNA: clinical features and management** 196
    Juan A. Pareja, Leopoldine A. Wilbrink, and María-Luz Cuadrado

21. **Hemicrania continua** 203
Johan Lim and Joost Haan

22. **Cluster tic syndrome and other combinations of primary headaches with trigeminal neuralgia** 208
Leopoldine A. Wilbrink, Joost Haan, and Juan A. Pareja

PART 4
Other primary short-lasting and rare headaches

23. **Primary stabbing headache** 215
Rashmi B. Halker, Esma Dilli, and Amaal Starling

24. **Cough headache** 220
Julio Pascual and Peter van den Berg†

25. **Exertional and sex headache** 225
Shih-Pin Chen, Julio Pascual, and Shuu-Jiun Wang

26. **Hypnic headache** 230
Dagny Holle and David W. Dodick

27. **Cranial neuralgias and persistent idiopathic facial pain** 237
Aydin Gozalov, Messoud Ashina, and Joanna M. Zakrzewska

28. **Some rare headache disorders, including Alice in Wonderland syndrome, blip syndrome, cardiac cephalalgia, epicrania fugax, exploding head syndrome, Harlequin syndrome, lacrimal neuralgia, neck–tongue syndrome, and red ear syndrome** 248
Randolph W. Evans

PART 5
Tension-type and other chronic headache types

29. **Tension-type headache: classification, clinical features, and management** 259
Stefan Evers

30. **New daily persistent headache** 267
Kuan-Po Peng, Matthew S. Robbins, and Shuu-Jiun Wang

31. **Chronic migraine and medication overuse headache** 275
David W. Dodick and Stephen D. Silberstein

32. **Frequent headaches with and without acute medication overuse: management and international differences** 284
Christina Sun-Edelstein and Alan M. Rapoport

33. **Nummular headache** 298
Juan A. Pareja and Carrie E. Robertson

PART 6
Secondary headaches: Diagnosis and treatment

34. **Thunderclap headache** 307
Hille Koppen, Agnes van Sonderen, and Sebastiaan F. T. M. de Bruijn

35. **Headache associated with head trauma** 314
Sylvia Lucas

36. **Cervicogenic headache** 322
Nikolai Bogduk

37. **Headache and neurovascular disorders** 334
Marieke J. H. Wermer, Hendrikus J. A. van Os, and David W. Dodick

38. **Headache attributed to spontaneous intracranial hypotension** 346
Farnaz Amoozegar, Esma Dilli, Rashmi B. Halker, and Amaal J. Starling

39. **Headache associated with high cerebrospinal fluid pressure** 356
Ore-ofe O. Adesina, Sudama Reddi, Deborah I. Friedman, and Kathleen Digre

40. **Headache associated with systemic infection, intoxication, or metabolic derangement** 367
Ana Marissa Lagman-Bartolome and Jonathan P. Gladstone

41. **Headache associated with intracranial infection** 384
Matthijs C. Brouwer and Jonathan P. Gladstone

42. **Remote causes of ocular pain** 392
Deborah I. Friedman

43. **Orofacial pain: dental head pains, temporomandibular disorders, and headache** 399
Steven B. Graff-Radford† and Alan C. Newman

44. **Headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL) syndrome** 403
Germán Morís and Julio Pascual

45. **Nasal and sinus headaches** 409
Vincent T. Martin and Maurice Vincent

46. **Giant cell arteritis and primary central nervous system vasculitis as causes of headache** 418
Mamoru Shibata, Norihiro Suzuki, and Gene Hunder

47. **Headache related to an intracranial neoplasm** 428
Elizabeth Leroux and Catherine Maurice

48. **Headache and Chiari malformation** 442
Dagny Holle and Julio Pascual

49. **Reversible cerebral vasoconstriction syndrome** 447
Aneesh B. Singhal

PART 7
Special topics

50. **Headaches in the young** 459
Vincenzo Guidetti, Benedetti Bellini, and Andrew D. Hershey

51. **Headaches in the elderly** 470
Jonathan H. Smith, Andreas Straube, and Jerry W. Swanson

52. **Headache and psychiatry** 475
Maurizio Pompili, Dorian A. Lamis, Frank Andrasik, and Paolo Martelletti

53. **Headache and hormones, including pregnancy and breastfeeding** 484
Sieneke Labruijere, Khatera Ibrahimi, Emile G.M. Couturier, and Antoinette Maassen van den Brink

54. **Headache and the weather** 494
Guus G. Schoonman, Jan Hoffmann, and Werner J. Becker

55. **Headache and sport** 502
David P. Kernick and Peter J. Goadsby

56. **Headache attributed to airplane travel** 508
Federico Mainardi and Giorgio Zanchin

57. **Headache and sleep** 514
Stefan Evers and Rigmor Jensen

58. **Headache and fibromyalgia** 523
Marina de Tommaso and Vittorio Sciruicchio

59. **Visual snow** 530
Gerrit L. J. Onderwater and Michel D. Ferrari

Index 535

Abbreviations

5-HT	5-hydroxytryptamine (serotonin)
[18F]-MPPF	[18F]-2'-methoxyphenyl-(N-2'-pyridinyl) -p-fluoro-benzamidoethyipiperazine
[18F]-FDG	fludeoxyglucose
AAION	arteritic anterior ischaemic optic neuropathy
AAN	American Academy of Neurology
ACE	angiotensin-converting enzyme
ACR	American College of Rheumatology
ACTH	adrenocorticotropic hormone
ADHD	attention-deficit hyperactivity disorder
AED	antiepileptic drug
AGES-Reykjavik	Age, Gene/Environment Susceptibility–Reykjavik study
AGS	Aicardi-Goutières syndrome
AH	airplane headache
AHC	alternating hemiplegia of childhood
AHI	apnoea/hypopnea index
AHS	American Headache Society
AIDS	acquired immune deficiency syndrome
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
AMPP	American Migraine Prevalence and Prevention Study
ARIC	Atherosclerosis Risk in Communities study
AR	allergic rhinitis
ARS	acute rhinosinusitis
ASA	acetylsalicylic acid
aSAH	aneurysmal subarachnoid haemorrhage
AUC	area under the curve
AVM	arteriovenous malformation
BBB	blood–brain barrier
BMI	body mass index
BOEP	benign occipital epilepsy of childhood with occipital paroxysms
BoNT-A	botulinum toxin type A
BPD	bipolar disorder
BPPV	benign paroxysmal positional vertigo
BSR	British Society for Rheumatism
CAD	cervical artery dissection
CADASIL	cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CAI	carbonic anhydrase inhibitor
CAMERA	Cerebral Abnormalities in Migraine, and Epidemiological Risk Analysis
cAMP	cyclic adenosine monophosphate
CBCT	cone beam computed tomography
CBF	cerebral blood flow
CBT	cognitive behavioural therapy
CBZ	carbamazepine
CCH	chronic cluster headache
CCL	chemokine (C-C motif) ligand
CCR7	C-C chemokine receptor type 7
CDH	chronic daily headache
cGMP	cyclic guanosine monophosphate
CGRP	calcitonin gene-related peptide
CHARM	CHronification And Reversibility of Migraine
CI	confidence interval
CM	chronic migraine
CM1	Chiari malformation type I
CNS	central nervous system
COCP	combined oral contraceptive pill
COL4	type IV collagen
COMOESTAS	Continuous Monitoring of Medication Overuse Headache in Europe and Latin America: development and STAndardization of an Alert and decision support System
COX	cyclooxygenase
CPAP	continuous positive airway pressure
CPCH	chronic post-craniotomy headache
CRP	C-reactive protein
CSD	cortical spreading depression
CSF	cerebrospinal fluid
CRS	chronic rhinosinusitis
CT	computed tomography
CTA	computed tomography angiography
CTM	computed tomography myelography
CTTH	chronic tension-type headache
CVST	cerebral venous sinus thrombosis
CXCL10	C-X-C motif chemokine ligand 10
DBF	dermal blood flow
DBS	deep brain stimulation
DHE	dihydroergotamine
DNA	deoxyribonucleic acid
dr-CCH	drug-refractory chronic cluster headache
DSA	digital subtraction angiography
DSM	digital subtraction myelography
DSM-5	*Diagnostic and Statistical Manual of Mental Disorders*, fifth edition
DWI	diffusion-weighted imaging
EA2	episodic ataxia type 2
EA6	episodic ataxia type 3
EAAT1	excitatory amino acid transporter 1
EBP	epidural blood patch
EBV	Epstein–Barr virus
ED	emergency department
EEG	electroencephalography
EFNS	European Federation of Neurological Societies
EM	episodic migraine

EPC	endothelial progenitor cell
ER	endoplasmic reticulum
ERα	oestrogen receptor alpha
ERβ	oestrogen receptor beta
ESR	erythrocyte sedimentation rate
EU	European Union
EULAR	European League Against Rheumatism
EVA	Epidemiology of Vascular Aging study
FASPS	familial advanced sleep phase syndrome
FCL	familial chilblain lupus
FDA	US Food and Drug Administration
FHM	familial hemiplegic migraine
FHM1	familial hemiplegic migraine type 1
FHM2	familial hemiplegic migraine type 2
FHM3	familial hemplegic migraine type 3
FLAIR	fluid-attenuated inversion recovery
FM	fibromyalgia
fMRI	functional magnetic resonance imaging
GABA	γ-aminobutyric acid
GCA	giant cell arteritis
GCS	Glasgow Coma Scale
GEFS+	generalized epilepsy with febrile seizures plus
GFR	glomerular filtration rate
GH	growth hormone
GnRH	gonadotropin-releasing hormone
GOM	granular osmiophilic material
GTN	glyceryl trinitrate
GWAS	genome-wide association studies
HANAC	hereditary angiopathy, nephropathy, aneurysms, and muscle cramps
HaNDL	headache and neurological deficits associated with CSF lymphocytosis
HC	hemicrania continua
HH	hypnic headache
Hib	*Haemophilus influenzae* type b
HIV	human immunodeficiency virus
HM	hemiplegic migraine
HR	hazard ratio
HRT	hormone replacement therapy
HUNT-3	Nord-Trøndelag Health Survey
IBMS	International Burden of Migraine Study
IBS	irritable bowel syndrome
ICA	internal carotid artery
ICH	intracerebral haemorrhage
ICHD	International Classification of Headache Disorders
ICHD-2	International Classification of Headache Disorders, second edition
ICHD-2R	International Classification of Headache Disorders, second edition revised
ICHD-3	International Classification of Headache Disorders, third edition
ICHD-3B	International Classification of Headache Disorders, third edition, beta version
ICD-10	Tenth Edition of the International Classification of Diseases
ICD-11	Eleventh Edition of the International Classification of Diseases
ICP	intracranial pressure
ICVD	International Classification of Vestibular Disorders
ID	Identify Migraine
ID-CM	Identify Migraine–Chronic Migraine
IEH	ictal epileptic headache
IFN	interferon
IGF-1	insulin-like growth factor 1
IHA	ictal headache
IHL	infratentorial hyperintense lesion
IIH	idiopathic intracranial hypertension
IIHTT	Idiopathic Intracranial Hypertension Treatment Trial
IL	interleukin
ILAE	International League Against Epilepsy
IM	intramuscular
IOI	idiopathic orbital inflammation
IPS	intermittent photic stimulation
IPSYS	Italian Project on Stroke in Young Adults
ITT	intention to treat
IV	intravenous
IVC	inferior vena cava
JBD	juvenile bipolar disorder
LAMI	low- and middle-income
LASIK	laser in situ keratomileusis
LDLPFC	left dorsolateral prefrontal cortex
LP	lumbar puncture
LPS	lumboperitoneal shunt
LSD	lysergic acid diethylamide
Mϕ	macrophage
MA	migraine with aura
mAb	monoclonal antibody
MARD	migraine anxiety-related dizziness
MBI	mindfulness-based intervention
MCM	major congenital malformation
MELAS	mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke
MI	myocardial infarction
MIDAS	Migraine Disability Assessment
MISP	mean intrasellar pressure
MIST	Migraine Intervention With STARFlex Technology
MMP	matrix metalloproteinase
MO	migraine without aura
MOH	medication overuse headache
MR	mixed rhinitis
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
MRM	menstrually related migraine
mRNA	messenger ribonucleic acid
mRS	modified Rankin Scale
MRV	magnetic resonance venography
MS	multiple sclerosis
mTBI	mild traumatic brain injury
mtDNA	mitochondrial DNA
MTHFR	methylenetetrahydrofolate reductase
MTT	mean transit time
NAR	non-allergic rhinitis
NDPH	new daily persistent headache
NH	nummular headache
NIH	National Institutes of Health
NNT	number needed to treat
NO	nitric oxide
NOMAS	Northern Manhattan Study
NREM	non-rapid eye movement
NSAID	non-steroidal anti-inflammatory drug

nVNS	non-invasive vagal nerve stimulation
OA	osteoarthritis
OCT	optical coherence tomography
ONS	occipital nerve stimulation
ONSF	optic nerve sheath fenestration
ONSTIM	Occipital Nerve Stimulation for the Treatment of Intractable Migraine
OR	odds ratio
OSAS	obstructive sleep apnoea syndrome
OTC	over-the-counter
OXC	oxcarbazepine
OXVASC	Oxford Vascular study
PACAP	pituitary adenylate cyclase-activating peptide
PACNS	primary angiitis of the central nervous system
PAG	periaqueductal gray
PCA	posterior cerebral artery
PCNSV	primary central nervous system vasculitis
PCR	polymerase chain reaction
PCS	post-concussion syndrome
PDGF	platelet-derived growth factor
PDPH	post-dural puncture headache
PedMIDAS	Pediatric Migraine Disability Assessment
PET	positron emission tomography
PFO	patent foramen ovale
PG	prostaglandin
PGE_2	prostaglandin E_2
PGI_2	prostaglandin I_2
PH	paroxysmal hemicrania
PHN	postherpetic neuralgia
PI3K	phosphoinositide 3-kinase
PIFP	persistent idiopathic facial pain
PIHA	pre-ictal headache
PMD	perimetric mean deviation
PMH	perimesencephalic subarachnoid haemorrhage
PMR	polymyalgia rheumatica
PNS	peripheral nerve stimulation
PO	per os
PPR	photoparoxysmal EEG response
PPV	positive predictive value
PREEMPT	Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy
PREMICE	PREvention of MIgraine using Cefaly
PRES	posterior reversible encephalopathy syndrome
PRISM	Precision Implantable Stimulator for Migraine
PROSPER	Prospective Study of Pravastatin in the Elderly At Risk
PSG	polysomnographic
PTCS	pseudotumour cerebri syndrome
PTH	post-traumatic headache
PWI	perfusion-weighted imaging
QP	quadripulse
RA	rheumatoid arthritis
RBC	red blood cell
RBD	REM sleep behaviour disorder
RCT	randomized controlled trial
RCVS	reversible cerebral vasoconstrictor syndrome
REM	rapid eye movement
RFT	radiofrequency thermocoagulation
RLS	restless legs syndrome
RNA	ribonucleic acid
RNFL	retinal nerve fibre layer
RPON	recurrent painful ophthalmoplegic neuropathy
rTMS	repeated-stimulation TMS
RVCL	retinal vasculopathy with cerebral leukodystrophy
RVCL-S	retinal vasculopathy with cerebral leukodystrophy and systemic manifestations
SAH	subarachnoid haemorrhage
SC	subcutaneous
SCA6	spinocerebellar ataxia type 6
SD	spreading depolarization
SE	status epilepticus
SHM	sporadic hemiplegic migraine
SIFAP1	Stroke in Young Fabry Patients
SIH	spontaneous intracranial hypotension
SLE	systemic lupus erythematosus
SMEI	severe myoclonic epilepsy of infancy
SNP	single nucleotide polymorphism
SNRI	serotonin and norepinephrine reuptake inhibitor
SNS	supraorbital nerve stimulation
SPECT	single-photon emission CT
SPG	sphenopalatine ganglion
SRHA	seizure-related headache
SSRI	selective serotonin reuptake inhibitor
sTMS	single-pulse TMS
STN	spinal trigeminal nucleus
SUNA	short-lasting unilateral neuralgiform headache attacks with cranial autonomic features
SUNHA	short-lasting unilateral neuralgiform headache attacks
SUNCT	short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing
TAB	temporal artery biopsy
TAC	trigeminal autonomic cephalgia
TBI	traumatic brain injury
TCH	thunderclap headache
tDCS	transcranial direct current stimulation
TED	thyroid eye disease
TENS	transcutaneous electrical nerve stimulation
T_H1	type 1 helper T cell
T_H17	type 17 helper T cell
THIN	The Health Improvement Network
TIA	transient ischaemic attack
TLR	Toll-like receptor
TM	transformed migraine
TMD	temporomandibular dysfunction
TMJ	temporomandibular joint
TMS	transcranial magnetic stimulation
TN	trigeminal neuralgia
TNC	trigeminal nucleus caudalis
TNF	tumour necrosis factor
TOV	transient obscurations of vision
TREX1	three prime repair exonuclease 1
TRT	total retinal thickness
tSNS	transcutaneous supraorbital nerve stimulator
TTH	tension-type headache
tVNS	transcutaneous supraorbital nerve stimulator
TVS	trigeminovascular system
VAS	visual analogue scale
VEGF	vascular endothelial growth factor
VEMP	vestibular evoked myogenic potential
VIP	vasoactive intestinal peptide

VNS	vagus nerve stimulation
VPS	ventriculoperitoneal shunt
vSMC	vascular smooth muscle cell
VZV	varicella zoster virus
WADA	World Anti-Doping Agency
WHO	World Health Organization
WHS	Women's Health Study
WML	white matter lesion

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PART 1

General introduction

1. **Classification and diagnosis of headache disorders** *3*
   Jes Olesen and Richard B. Lipton
2. **Taking a headache history: tips and tricks** *12*
   James W. Lance and David W. Dodick
3. **Diagnostic neuroimaging in migraine** *17*
   Mark C. Kruit and Arne May
4. **Headache mechanisms** *34*
   Andrew Charles
5. **Headache in history** *45*
   Mervyn J. Eadie

1

Classification and diagnosis of headache disorders

Jes Olesen and Richard B. Lipton

Introduction

Disease classification systems delineate a group of related disorders and provide operational rules for defining the boundaries among them. Diagnosis refers to the assignment of a particular individual to a particular diagnostic category (1). A robust disease classification system provides a framework for standardizing diagnosis, studying epidemiology, predicting prognosis, assessing treatment, and implementing therapy in practice (2). Disease classification is therefore crucial for both clinical practice and research.

The first modern attempt to classify headache disorders was undertaken by the National Institutes of Health (NIH) in the United States in 1962 (NIH classification) (3). This classification described 15 headache disorders but was neither operational nor evidence-based. Operational criteria identify features, or combinations of features, that establish or exclude a particular diagnosis. In the NIH classification, migraine was defined as a subtype of vascular headache characterized by recurrent headache, of various durations, intensity, and frequency, usually unilateral, associated with nausea/vomiting and sensory, motor, and mood disturbances (3). This language is not specific; as a consequence, two clinicians may assign different diagnoses to the same patient using these criteria.

The International Classification of Headache Disorders (ICHD), now in its third edition, was designed to address the limitations of the NIH classification. First published in 1988 (4), all editions of the ICHD provide operational diagnostic criteria for a broad range of headache disorders. The second edition, ICHD-2 (5), was published in 2004 and ICHD-3 (6) was published in 2013. All editions have been translated into multiple languages. The ICHD also provides a common language, which facilitates communication worldwide. ICHD-based diagnoses have been used to study epidemiology, natural history, biology, and treatment, leading to many advances in headache medicine. This research has been the foundation for treatment guidelines developed in many countries. Throughout this period, the ICHD system has remained the undisputed gold standard for headache classification.

ICHD-3 was published in a 'beta' version, to facilitate field-testing. Because the classification committee anticipated that changes in the final version of ICHD-3 would be minor, they encouraged immediate use of the beta version both in practice and in research. Publication of the final ICHD-3 was coordinated with release of the eleventh edition of the International Classification of Diseases (ICD-11) from the World Health Organization (WHO). Early adoption of ICHD-3 by clinicians generated familiarity and ease of use of the ICD-11. In this chapter, we will review some of the important aspects of the ICHD-3 classification and then discuss an approach to its application in clinical practice.

The ICHD-3 system has continuity with earlier versions

All versions of the ICHD system have many features in common. The basic structure and format of the diagnostic criteria remain unchanged. The ICHD-3 criteria define three major categories of disorders: primary headaches; secondary headaches; and cranial neuralgias and facial pain (4–6). For primary headache disorders, the headache disorder is the problem; the clinical profile is a manifestation of a condition with a unique pathogenesis, such as migraine with aura or cluster headache. For secondary headache disorders, headaches are attributed to an underlying condition such as a disease, trauma, or a drug. Cranial neuralgias and face pain are a distinctive set of disorders described further on in this chapter.

The classification specifies that many individuals have more than one type of headache. As a consequence, each type of headache should be diagnosed. Some individuals may have two primary headache disorders (migraine and tension-type headache). Others may have a primary headache disorder and a secondary headache disorder (chronic migraine and medication overuse headache). Still others may have a primary headache disorder and a cranial neuralgia (migraine with aura and trigeminal neuralgia). Diagnosis can be difficult in a patient

with more than one disorder as they may not classify their headache experiences in the same way a headache specialist might.

The ICHD system in all of its incarnations is hierarchical, organizing diagnostic entities into major categories with several levels of subcategories, denoted by a multidigit codes (4–6). As a consequence, diagnoses can be assigned with a level of precision appropriate to the diagnostic setting. In general practice, a two-digit code may suffice (e.g. migraine without aura). In neurological practice, two- or three-digit codes can be used. In headache practice or research, additional digits of diagnostic coding allow even greater precision. These hierarchical diagnoses make the ICHD system flexible and broadly applicable to a range of settings and purposes.

For both primary and secondary headache disorders diagnostic criteria comprise a series of lettered headings, each of which must be fulfilled to make a diagnosis. Often, the lettered criteria can be met in several ways (i.e. two of four pain features), a structure termed 'polythetic'. Other letter headings can only be fulfilled in a single way, a structure termed 'monothetic'.

Several kinds of features are not generally used in diagnostic criteria. Inheritance is usually avoided as that would create circularity in studies of familial aggregation. Treatment responses are also typically not used as no treatment works in every patient with a particular disorder. Requiring a response to a single drug makes diagnosis difficult in patients unable to take that drug. In addition, including treatment as part of the case definition may interfere with the development of alternative treatments. The only exceptions to this rule are the requirement for an indomethacin response in patients with certain indomethacin-responsive disorders, such as hemicrania continua. The hope is that these exceptions will be replaced by better operational rules not based on treatment response, as classification science advances.

Box 1.1 Criteria for migraine with aura

- **A** At least two attacks fulfilling criteria B and C.
- **B** One or more of the following fully reversible aura symptoms:
  - **1** Visual
  - **2** Sensory
  - **3** Speech and/or language
  - **4** Motor
  - **5** Brainstem
  - **6** Retinal.
- **C** At least three of the following six characteristics:
  - **1** At least one aura symptom spreads gradually over ≥5 minutes
  - **2** Two or more aura symptoms occur in succession
  - **3** Each individual aura symptom lasts 5–60 minutes[1]
  - **4** At least one aura symptom is unilateral[2]
  - **5** At least one aura symptom is positive[3]
  - **6** The aura is accompanied, or followed within 60 minutes, by headache.
- **D** Not better accounted for by another ICHD-3 diagnosis.

Notes

1 When, for example, three symptoms occur during an aura, the acceptable maximal duration is 3 × 60 minutes. Motor symptoms may last up to 72 hours.

2 Aphasia is always regarded as a unilateral symptom; dysarthria may or may not be.

3 Scintillations and pins and needles are positive symptoms of aura.

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Changes in the ICHD-3 classification of primary headache disorders

The ICHD-3 classification includes important changes for the classification of migraine with aura, chronic migraine (CM), hemicrania continua, nummular headache, hypnic headache, new daily persistent headache (NDPH), primary stabbing headache, and primary thunderclap headache (6). We will consider these changes one at a time. Criteria for migraine without aura and tension-type headache remain unaltered and will not be discussed.

Changes in the classification of migraine

Migraine with aura

Migraine with aura (1.2) is now defined at the two-digit level using the criteria specified in Box 1.1. Specific subtypes of migraine with aura are defined at the third digit level.

Chronic migraine

Classification of CM has been very controversial (7). In the ICHD-3, CM was moved from the Appendix to the main body of the classification, based on the criteria shown in Box 1.2. In the revision, CM and medication overuse headache can be diagnosed in patients who meet criteria for both disorders—a crucial change from ICHD-2.

In the ICHD-2, CM could not be diagnosed in the presence of acute medication overuse (5). This rule was modified for a number of reasons and is consistent with one of the pre-existing classification rules: if a primary headache disorder is made significantly worse (at least a doubling of headache days) by a secondary cause, then both the primary headache and the secondary headache should be diagnosed and coded. In addition, CM and medication overuse headache occur together with a very high frequency, both in clinic-based and population studies (8,9). Medication overuse is a risk factor the development of CM in a person with episodic migraine (EM) (10). In a patient with CM and medication overuse headache, if medication withdrawal is associated with a reversion of CM to EM (<15 headache days per month), then the diagnosis would change to episodic migraine. The separation of migraine into a chronic and an episodic form has been criticized because headache days per month varies within patients with migraine over time. Nonetheless, it is important to distinguish this severely affected group of patients, who require intensive treatment. In addition, there are differences among persons with EM and CM in terms of epidemiology, imaging, and treatment response.

Familial hemiplegic migraine

Familial hemiplegic migraine can be subtyped based on specific genetic abnormalities (11). In this sense the disorder is the only primary headache attributed to an underlying cause.

Vestibular migraine

Vestibular migraine is included in the appendix with diagnostic criteria developed in collaboration with the Barany Society. They will serve a useful purpose in the further exploration of this enigmatic and disputed entity.

Box 1.2 Criteria for chronic migraine

- **A** Headache (migraine-like or tension-type-like)[1] on ≥15 days/month for >3 months, and fulfilling criteria B and C.
- **B** Occurring in a patient who has had at least five attacks fulfilling criteria B–D for 1.1 *Migraine without aura* and/or criteria B and C for 1.2 *Migraine with aura*.
- **C** On ≥8 days/month for >3 months, fulfilling any of the following:[2]
  - **1** Criteria C and D for 1.1 *Migraine without aura*.
  - **2** Criteria B and C for 1.2 *Migraine with aura*.
  - **3** Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.
- **D** Not better accounted for by another ICHD-3 diagnosis.[3–5]

Notes

1. The reason for singling out '1.3 *Chronic migraine*' from types of episodic migraine is that it is impossible to distinguish the individual episodes of headache in patients with such frequent or continuous headaches. In fact, the characteristics of the headache may change not only from day to day, but even within the same day. Such patients are extremely difficult to keep medication-free in order to observe the natural history of the headache. In this situation, attacks with and those without aura are both counted, as are both migraine-like and tension-type-like headaches (but not secondary headaches).
2. Characterization of frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day-by-day for at least one month.
3. Because tension-type-like headache is within the diagnostic criteria for '1.3 Chronic migraine', this diagnosis excludes the diagnosis of '2. Tension-type headache' or its types.
4. '4.10 New daily persistent headache' may have features suggestive of '1.3 Chronic migraine'. The latter disorder evolves over time from '1.1 Migraine without aura' and/or '1.2 Migraine with aura'; therefore, when these criteria A–C are fulfilled by headache that, unambiguously, is daily and unremitting from <24 hours after its first onset, code as '4.10 New daily persistent headache'. When the manner of onset is not remembered or is otherwise uncertain, code as '1.3 Chronic migraine'.
5. The most common cause of symptoms suggestive of chronic migraine is medication overuse, as defined under '8.2 Medication-overuse headache'. Around 50% of patients apparently with '1.3 Chronic migraine' revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed as '1.3 Chronic migraine'. Equally, many patients apparently overusing medication do not improve after drug withdrawal; the diagnosis of '8.2 Medication-overuse headache' may be inappropriate for these (assuming that chronicity induced by drug overuse is always reversible). For these reasons, and because of the general rule to apply all relevant diagnoses, patients meeting criteria for '1.3 Chronic migraine' and for '8.2 Medication-overuse headache' should be coded for both. After drug withdrawal, migraine will either revert to an episodic type or remain chronic, and should be re-diagnosed accordingly; in the latter case, the diagnosis of '8.2 Medication-overuse headache' may be rescinded.

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Hemicrania continua

Hemicrania continua has been moved from Chapter 4 (*Other Primary Headaches*) to Chapter 3 (*Trigeminal Autonomics Cephalgias*). This change is justified by the fact that hemicrania continua and the other trigeminal autonomic cephalgias are characterized by trigeminal pain and ipsilateral autonomic features (12).

Box 1.3 Criteria for nummular headache

- **A** Continuous or intermittent head pain fulfilling criterion B.
- **B** Felt exclusively in an area of the scalp, with three of the following four characteristics:
  - **1** Sharply-contoured
  - **2** Fixed in size and shape
  - **3** Round or elliptical
  - **4** 1–6 cm in diameter.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Nummular headache

Nummular headache was added to Chapter 4. This entity is characterized by a 'coin-shaped' spot on the scalp, often in parietal head regions (**Box 1.3**).

Nummular headache may arise as a response to trauma or surgery but most often occurs spontaneously (13). It is relatively rare but may be severe and debilitating.

Primary headache associated with sexual activity

The criteria for primary headache associated with sexual activity have been simplified. The division into pre-orgasmic headache and orgasmic headache is not supported by prospective studies (14–16).

Hypnic headache

Although hypnic headache retains its onset during sleep, the criterion based on age has been removed, as have the requirements for severity and type of headache (**Box 1.4**).

New daily persistent headache

The criteria for NDPH have changed markedly (6,17,18). The diagnostic criteria focus exclusively on the sudden onset within 24 hours of a continuous headache, which must have been present for at least three months and is not better accounted for by another diagnosis (**Box 1.5**).

Primary stabbing headache

Primary stabbing headache has refined criteria, which are presented in **Box 1.6** (19).

Primary thunderclap headache

Primary thunderclap headache has headache features identical to those of headache attributable to subarachnoid haemorrhage but

Box 1.4 Criteria for hypnic headache

- **A** Recurrent headache attacks fulfilling criteria B–E.
- **B** Developing only during sleep, and causing wakening.
- **C** Occurring on ≥10 days per month for >3 months.
- **D** Lasting from 15 minutes up to 4 hours after waking.
- **E** No cranial autonomic symptoms or restlessness.
- **F** Not better accounted for by another ICHD-3 diagnosis.

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Box 1.5 Criteria for new daily persistent headache

- **A** Persistent headache fulfilling criteria B and C.
- **B** Distinct and clearly remembered onset, with pain becoming continuous and unremitting within 24 hours.
- **C** Present for >3 months.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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without evidence of such haemorrhage. This is a diagnosis of inclusion that requires a very specific clinical phenotype, described in Box 1.7, and a diagnosis of exclusion, in that underlying causes have to ruled out by extensive investigation, including magnetic resonance imaging or computed tomography angiography and venography (20).

Part of the problem may be in the definition of the primary thunderclap headache. Diagnostic criteria require that headache be maximal within 1 minute. The impression is that the true time from onset to peak intensity (i.e. as opposed to the use of the word 'sudden', for example) is not always accurately elicited in emergency departments and therefore headaches that take longer to develop may mistakenly be categorized as primary thunderclap headache. Future prospective studies regarding this issue are necessary.

Changes to the ICHD-3 classification of secondary headache

In the ICHD-2, a secondary headache diagnosis became definite if the headache disappeared or greatly improved, either spontaneously or following treatment of the secondary cause. The general format for secondary headache disorders in the ICHD-3 are summarized in Box 1.8 (16).

Remission of headache with improvement of the causative disorder is not a reliable sole diagnostic criterion for secondary headache. Headache may persist after trauma for more than 3 months (21), and parallel patterns may occur with other secondary headache disorders. The temporal relationship of headache onset and remission in relation to the emergence and remission of disorders thought to cause secondary headache is a fertile area for future research.

Box 1.6 Criteria for primary stabbing headache

- **A** Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B–D.
- **B** Each stab lasts for up to a few seconds.
- **C** Stabs recur with irregular frequency, from one to many per day.
- **D** No cranial autonomic symptoms.
- **E** Not better accounted for by another ICHD-3 diagnosis.

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Box 1.7 Criteria for primary thunderclap headache

- **A** Severe head pain fulfilling criteria B and C.
- **B** Abrupt onset, reaching maximum intensity in <1 minute.
- **C** Lasting for ≥5 minutes.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Headache attributed to trauma or injury to the head and/or neck

Chronic post-traumatic headache was renamed 'persistent headache attributed to traumatic injury to the head' to parallel the naming of other secondary headache disorders. The criteria require headache onset within 7 days of trauma or within 7 days of becoming able to communicate the history clearly (21). As the period of increased risk of headache onset following head injury is uncertain, the Appendix provides criteria for delayed onset persisting headache attributed to traumatic injury.

Headache attributed to cranial or cervical vascular disorder

Accumulating evidence confirms that headache is a frequent symptom of many types of cerebrovascular disorders, including disease of large and small arteries, veins, and dural sinuses. Based on accumulating knowledge, disorders have been regrouped and names have been changed. The term reversible cerebral vasoconstrictor syndrome (RCVS) is now applied to the disorder previously known as benign vasculopathy of the brain (Box 1.9) (20).

The disorder is often benign but may be associated with posterior reversible encephalopathy syndrome, arterial dissection, and ischaemic and haemorrhagic stroke (20,22–25). If recurrent thunderclap headaches occur in the absence of other causes, a diagnosis of RCVS should be considered. RCVS may be responsive to oral or parenteral calcium channel blockers.

Box 1.8 Criteria for general diagnostic criteria for secondary headaches

- **A** Any headache fulfilling criterion C.
- **B** Another disorder scientifically documented to be able to cause headache has been diagnosed. Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of the presumed causative disorder
  - **2** One or both of the following:
    - headache has significantly worsened in parallel with worsening of the presumed causative disorder
    - headache has significantly improved in parallel with improvement of the presumed causative disorder
  - **3** Headache has characteristics typical for the causative disorder
  - **4** Other evidence exists of causation.
- **C** Not better accounted for by another ICHD-3 diagnosis.

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Box 1.9 Criteria for headache attributed to reversible cerebral vasoconstriction syndrome (RCVS)

- **A** Any new headache fulfilling criterion C.
- **B** RCVS has been diagnosed.
- **C** Evidence of causation demonstrated by at least one of the following:
  - **1** Headache, with or without focal deficits and/or seizures, has led to angiography (with 'strings and beads' appearance) and diagnosis of RCVS
  - **2** Headache has either or both of the following characteristics:
    - recurrent during ≤1 month, and with thunderclap onset
    - triggered by sexual activity, exertion, Valsalva manoeuvers, emotion, bathing and/or showering
  - **3** No new significant headache occurs >1 month after onset.
- **D** Not better accounted for by another ICHD-3 diagnosis, and aneurysmal subarachnoid haemorrhage has been excluded by appropriate investigations.

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Box 1.10 Criteria for headache attributed to idiopathic intracranial hypertension (IIH)

- **A** New headache, or a significant worsening[1] of a pre-existing headache, fulfilling criterion C.
- **B** Both of the following:
  - **1** Idiopathic intracranial hypertension (IIH) has been diagnosed[2]
  - **2** Cerebrospinal fluid (CSF) pressure exceeds 250 mm CSF (or 280 mm CSF in obese children)[3]
- **C** Either or both of the following:
  - **1** Headache has developed or significantly worsened in temporal relation to the IIH, or led to its discovery
  - **2** Headache is accompanied by either or both of the following:
    - pulsatile tinnitus
    - papilledema[4]
- **D** Not better accounted for by another ICHD-3 diagnosis.[5,6]

Notes

1 'Significant worsening' implies a twofold or greater increase in frequency and/or severity in accordance with the general rule on distinguishing secondary from primary headache.

2 IIH should be diagnosed with caution in those with altered mental status.

3 For diagnostic purposes, CSF pressure should be measured in the absence of treatment to lower intracranial pressure. CSF pressure may be measured by lumbar puncture performed in the lateral decubitus position without sedative medications or by epidural or intraventricular monitoring. Because CSF pressure varies during the course of a day, a single measurement may not be indicative of the average CSF pressure over 24 hours: prolonged lumbar or intraventricular pressure monitoring may be required in cases of diagnostic uncertainty.

4 Papilloedema must be distinguished from pseudopapilloedema or optic disc oedema. The majority of patients with IIH have papilloedema, and IIH should be diagnosed with caution in patients without this sign.

5 '7.1.1 Headache attributed to idiopathic intracranial hypertension' may mimic the primary headaches, especially '1.3 Chronic migraine' and '2.3 Chronic tension-type headache'; on the other hand, these disorders commonly co-exist with IIH.

6 82 Medication-overuse headache should be excluded in patients lacking papilloedema, abducens palsy or the characteristic neuroimaging signs of IIH.

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Headache attributed to arterial dissection was well defined in the ICHD-2, but evidence supporting this entity has accumulated (26). Some rare disorders have been assembled under the title *headache attributed to genetic vasculopathy*.

Headache attributed to non-vascular intracranial disorder

Criteria were revised for a number of disorders in this broad chapter.

Idiopathic intracranial hypertension

The revised criteria for idiopathic intracranial hypertension (IIH) are provided in Box 1.10. The criteria no longer require specific headache features, headache relief with removal of cerebrospinal fluid (CSF), or the presence of papilloedema. To make the diagnostic criteria more specific, the requisite opening pressure on lumbar puncture was raised to 250 mm water. It was also noted that in some people, particularly children, normal opening pressures may be as high as 280 mm water. Body mass index-stratified criteria for opening pressure were removed. By not requiring papilloedema, the classification acknowledges that IIH without papilloedema can exist; a position held among experts and corroborated by the literature (27–29). The neuroimaging findings associated with IIH are acknowledged (empty sella turcica, distension of the peri-optic subarachnoid space, flattening of the posterior sclerae, and protrusion of the optic nerve papillae into the vitreous) but not part of the formal criteria (30).

Headache associated with spontaneous (or idiopathic) low CSF pressure

Criteria for low-pressure headache were changed as indicated in Box 1.11. Requirements for orthostatic headache associated with specific symptoms were dropped because CSF leaks occur in the absence of a postural headaches (31,32). Now the diagnosis requires any headache associated with low CSF pressure or imaging findings that document a CSF leak.

Headache and neurological deficits associated with CSF lymphocytosis

Revised criteria emphasize that headache and neurological deficits associated with CSF lymphocytosis (HaNDL) is associated with sensory, language, or motor deficits that last four or more hours in contrast with the typically shorter-lived deficits that typify transient ischaemia attacks and migraine with aura (Box 1.12).

Headache attributed to a Chiari malformation type 1

Criteria for headache attributed to Chiari malformation type 1 are provided in Box 1.13. The criteria require short-lived headache, lasting less than 5 minutes, provocation by Valsalva, or posterior

Box 1.11 Criteria for headache attributed to low cerebrospinal fluid pressure

- **A** Any headache fulfilling criterion C.
- **B** Either or both of the following:
  - **1** Low cerebrospinal fluid (CSF) pressure (<60 mm CSF)
  - **2** Evidence of CSF leakage on imaging.
- **C** Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or led to its discovery.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 1.12 Criteria for syndrome of transient headache and neurological deficits with cerebrospinal fluid lymphocytosis (HaNDL)

- **A** Episodes of migraine-like headache fulfilling criteria B and C.
- **B** Both of the following:
  - **1** Accompanied or shortly preceded by the onset of at least one of the following transient neurological deficits lasting >4 hours
    - hemiparaesthesia
    - dysphasia
    - hemiparesis.
  - **2** Associated with cerebrospinal fluid (CSF) lymphocytic pleocytosis (>15 white cells per μl), with negative aetiological studies.
- **C** Evidence of causation demonstrated by either or both of the following:
  - **1** Headache and transient neurological deficits have developed or significantly worsened in temporal relation to onset or worsening of the CSF lymphocytic pleocytosis, or led to its discovery
  - **2** Headache and transient neurological deficits have significantly improved in parallel with improvement in the CSF lymphocytic pleocytosis.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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location. As Chiari malformations may be incidental, characterizing the headache may help avoid unnecessary decompressive surgery. An important differential diagnostic point is that tonsillar descent may occur in low-pressure headache.

Headache attributed to a substance or its withdrawal

The requirements in the ICHD-2 for changes in headache days in relation to changes in medication taking were removed, because they were difficult to ascertain and hard to interpret. Medication overuse headache is now diagnosed in all patients who take medication at a level that exceeds specified limits if they have a primary headache that occurs on 15 or more days per month (Box 1.14).

Box 1.13 Criteria for headache attributed to Chiari malformation type I

- **A** Headache fulfilling criterion C.
- **B** Chiari malformation type 1 (CM1) has been demonstrated.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Either or both of the following:
    - headache has developed in temporal relation to the CM1 or led to its discovery
    - headache has resolved within 3 months after successful treatment of the CM1
  - **2** Headache has at least one of the following three characteristics:
    - precipitated by cough or other Valsalva-like manoeuvre
    - occipital or suboccipital location
    - lasting <5 minutes
  - **3** Headache is associated with other symptoms and/or clinical signs of brainstem, cerebellar, lower cranial nerve and/or cervical spinal cord dysfunction.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 1.14 Criteria for medication-overuse headache

- **A** Headache occurring on ≥15 days per month in a patient with a pre-existing headache disorder.
- **B** Regular overuse for >3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.
- **C** Not better accounted for by another ICHD-3 diagnosis.

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Acute headache induced by substances have emerged as important experimental models providing insights into the mechanisms of migraine. In particular, calcitonin gene-related peptide (CGRP)-induced headache is important because it was a major stimulus for the development of CGRP receptor antagonists and CGRP antibodies for the acute and preventive treatment of migraine, respectively.

Headache attributed to disorder of homeostasis

The criteria for high-altitude headache were refined based on recent papers (33,34). Headache attributed to airplane travel has been added to the ICHD-3 (Box 1.15) (35).

By definition, these headaches occur during plane travel and arise or remit during take-off, or, in the vast majority of cases, during landing. Criterion D requires the exclusion of sinus disorders.

Headache attributed to sleep apnoea was retained in the ICHD-3, but the published evidence supporting its existence is considered weak.

Headache attributed to autonomic dysreflexia

Headache attributed to autonomic dysreflexia, a new disorder, occurs in patients with spinal cord injury. The headache is of sudden onset and diffuse, typically associated with autonomic symptoms, including a rise in blood pressure often accompanied by bladder or bowel symptoms (36,37). Triggers include bladder distention, urinary tract infection, bowel distention or impaction, or urological

Box 1.15 Criteria for headache attributed to airplane travel

- **A** At least two episodes of headache fulfilling criterion C.
- **B** The patient is travelling by airplane.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed exclusively during airplane travel
  - **2** Either or both of the following:
    - headache has worsened in temporal relation to ascent after take-off and/or descent prior to landing of the aeroplane
    - headache has spontaneously improved within 30 minutes after the ascent or descent of the aurplane is completed
  - **3** Headache is severe, with at least two of the following three characteristics:
    - unilateral location
    - orbitofrontal location (parietal spread may occur)
    - jabbing or stabbing quality (pulsation may also occur).
- **D** Not better accounted for by another ICHD-3 diagnosis.

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procedures, among others. The dysautonomia can be life threatening. Exclusion of RCVS is important (36).

Headache or facial pain attributed to disorder of the cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cervical structures

This chapter was minimally revised as new data are lacking.

Cervicogenic headache

Criteria for cervicogenic headache in the ICHD-2 required definite structural lesions in the cervical spine. The criteria have now been broadened to include soft tissues of the neck and not exclude tenderness of cervical muscles (Box 1.16).

As tension-type headache may arise from the myofascial tissues in the head and/or neck distinguishing these disorders may be problematic. *Headache attributed to cervical myofascial tenderness* has been added to the Appendix, adding additional complexity. If the source of pain is in the muscle, then tension-type headache is the preferred diagnosis. The overlap of these disorders represents an important area for future research.

Headache attributed to temporomandibular disorder

The diagnostic criteria for headache attributed to temporomandibular disorder are shown in Box 1.17.

If there are abnormalities of the temporomandibular joint then the diagnosis can be straightforward. If the only abnormality is tenderness of the muscles of mastication it may be difficult to distinguish this disorder from tension-type headache. Strongly held positions and regional dogmatic tradition continue to impede a solution to these issues.

Headache attributed to psychiatric disorder

This chapter remains essentially unchanged as almost no new evidence has appeared. It is, however, the opinion of the experts that psychiatric disorders, particularly depression and anxiety, may be a cause of headache. A large section in the Appendix concerning headache attributed to psychiatric disorder is designed to stimulate research.

Box 1.16 Criteria for cervicogenic headache

- **A** Any headache fulfilling criterion C.
- **B** Clinical and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion
  - **2** Headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion
  - **3** Cervical range of motion is reduced and headache is made significantly worse by provocative manoeuvres
  - **4** Headache is abolished following diagnostic blockade of a cervical structure or its nerve supply.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 1.17 Criteria for headache attributed to temporomandibular disorder

- **A** Any headache fulfilling criterion C.
- **B** Clinical evidence of a painful pathological process affecting elements of the temporomandibular joint(s), muscles of mastication, and/or associated structures on one or both sides.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of the temporomandibular disorder
  - **2** The headache is aggravated by jaw motion, jaw function (e.g. chewing) and/or jaw parafunction (e.g. bruxism)
  - **4** The headache is provoked on physical examination by temporalis muscle palpation and/or passive movement of the jaw.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Cranial neuralgias and facial pain

This chapter has been considerably revised in collaboration with colleagues from the International Association for the Study of Pain.

Classical trigeminal neuralgia

Firstly, we consider the new criteria for classical trigeminal neuralgia (Box 1.18).

These criteria are very specific, although specificity may have been achieved at the price of sensitivity. A patient whose pain radiates outside the trigeminal distribution may respond to trigeminal neuralgia therapy. Similarly, although the criteria require the absence of a neurological deficit, using quantitative sensory testing, documented

Box 1.18 Criteria for trigeminal neuralgia

Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond,[1] and fulfilling criteria B and C.

- **A** Pain has all of the following characteristics:
  - **1** Lasting from a fraction of a second to 2 minutes[2]
  - **2** Severe intensity[3]
  - **3** Electric shock-like, shooting, stabbing, or sharp in quality.
- **B** Precipitated by innocuous stimuli within the affected trigeminal distribution.[4]
- **C** Not better accounted for by another ICHD-3 diagnosis.

Notes

- **1** In a few patients, pain may radiate to another division, but it remains within the trigeminal dermatomes.
- **2** Duration can change over time, with paroxysms becoming more prolonged. A minority of patients will report attacks predominantly lasting for > 2 minutes.
- **3** Pain may become more severe over time.
- **4** Some attacks may be, or appear to be, spontaneous, but there must be a history or finding of pain provoked by innocuous stimuli to meet this criterion. Ideally, the examining clinician should attempt to confirm the history by replicating the triggering phenomenon. However, this may not always be possible because of the patient's refusal, awkward anatomical location of the trigger and/or other factors.

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sensory abnormalities in the affected area are not rare in classical trigeminal neuralgia (38).

Ophthalmoplegic migraine

Ophthalmoplegic migraine is no longer in the migraine chapter and is instead regarded as a cranial neuropathy, although this decision remains controversial (39–43).

Persistent idiopathic facial pain

Atypical facial pain is now called 'persistent idiopathic facial pain'. This disorder is characterized by constant boring, burning, pressing facial pain, which contrasts with the electrical, paroxysmal, stabbing, and radiating quality of trigeminal neuralgia. Drugs known to be effective for classical trigeminal neuralgia are generally not effective.

Relation to the ICD-11 and validity testing

Work on the ICHD-3 began before the major structure of the ICD-11 was decided by the WHO. The WHO has long recognized the enormous importance of headache disorders, as reflected by their Global Burden of Disease study, demonstrating that migraine is the seventh most disabling medical illness in the world (44). The same study shows that headache is the world's most disabling neurological disease (44).

Given their emphasis on common disorders and diagnosis in general practice, headache disorders are very important to the development of the ICD-11. WHO representatives agreed to use the ICHD-3 in a simplified form. In the neurology section of the ICD-11, headache disorders have their own section and all primary headaches are included. The important secondary headaches are also included using cross reference to the causative disorder. This is of tremendous importance to the fields of neurology and headache medicine as all headache disorders will be classified in the neurology chapter.

Field testing of the ICHD-3 will occur in collaboration with the WHO as they test the ICD-11. The emphasis will be on the clinical utility of ICD-11 in comparison with the ICD-10, based on the evaluation of case vignettes presented online. Field testing will include physicians from all fields including headache experts. Systematic data will be used to determine whether all patients can be classified (completeness) and whether clinicians evaluating the same vignette assign the same diagnosis or diagnoses (reliability). Validity will be examined using demographic profile, disability, family history, treatment response, comorbidities, and biomarkers as external validators. Generalizability will be assessed by applying the criteria to patients from different settings such as primary care, neurological practice, and headache specialty practice.

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2

Taking a headache history

Tips and tricks

James W. Lance and David W. Dodick

Introduction

Long before the arrival of computed tomography and magnetic resonance scanning, the most useful diagnostic tool was freely available—a comprehensive case history.

Clinicians vary the order in which they take a history, but it does not matter as long as it covers all the important points that define clearly the pattern of headache, helping to place symptoms in an appropriate group for diagnostic purposes.

If the headaches are of recent onset or there is a dramatic single episode like a thunderclap headache or acute head injury, we may wish to enquire first about the patient's past health, family history, and personal background before obtaining a detailed description of the incident and headache characteristics. One then has a mental picture of the patient's life before the onset of headache and can compare this with their life afterwards.

More often, when headaches are recurrent and their frequency has progressively increased we prefer to establish the evolution of the headache before dealing with the patient's past health, and genetic and social background.

The headache history

If the patient has more than one type of headache, such as the common combination of migraine and tension-type headache, each should be analysed separately.

A template is now suggested.

Length of illness

- Acute: hours or days.
- Subacute: weeks or months.
- Chronic: years (chronic is used in a more specific sense in 'chronic migraine' to indicate 15 or more migraine-like headaches each month).

Frequency and duration of headaches

These characteristics establish the temporal pattern of headaches. Check that the answers make sense. Four headaches a week, each lasting 2 days, does not compute, whereas many attacks in a single day, each lasting minutes to hours, may reflect accurately the pattern of cluster headache and other trigeminal autonomic cephalgias (TACs) (**Figure 2.1**).

Time and mode of onset

Premonitory symptoms:

Many migrainous patients recall familiar sensations the evening before awakening with a headache the next morning, or in the hours preceding a headache such as:

- neck stiffness;
- yawning;
- drowsiness;
- a sense of elation;
- hunger;
- a craving to eat chocolate or other sweet foods.

The sequence of a morning headache following eating chocolate is sometimes mistaken for chocolate being a trigger factor, whereas craving for chocolate may be the first symptom of a migraine attack.

These are clear markers for migraine and their recognition opens the way for nocturnal medication to prevent a headache developing the following day, or earlier treatment with acute migraine therapies.

Aura:

Aura symptoms may include visual, sensory, language, motor, or vestibular dysfunction.

The most common aura is a visual disturbance, a zig zag shimmering 'fortification spectrum' (teichopsia), affecting some 10% of migrainous patients, with unformed flashes of light (photopsia) being experienced by another 25%. Fortification spectra usually move slowly across a visual half field for 10–60 minutes, leaving an area of impaired vision behind them. They usually precede the onset of headache but may persist until the headache fades, appear during headache, or even without headache as a relatively uncommon 'migraine equivalent' (acephalgic migraine) (**Figure 2.2**). Paraesthesia, aphasia, and hemiparesis may also form part of the aura (1). The feature of migraine equivalents that distinguishes them from transient ischaemic attacks is their slow progressive march over the visual fields or body and leisurely disappearance.

Headache characteristics

Headache can be either unilateral or bilateral in migraine patients but is unilateral in nearly all those with cluster headache, TACs,

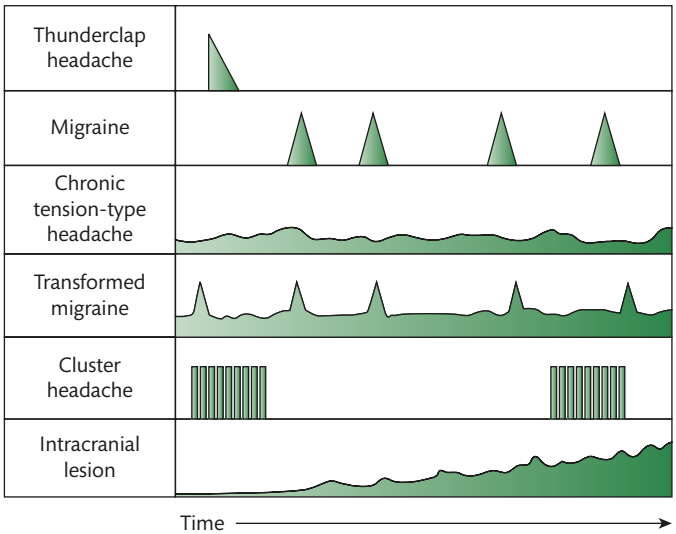

Figure 2.1 Temporal patterns of headache.
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trigeminal neuralgia, and, by definition, all those with hemicrania continua (Figure 2.3). Pain in cluster headache is usually felt deep behind one eye. If the pain is felt mainly below the eye it is known as 'lower half headache' or facial migraine and may be confused with sinusitis. Many migraine patients with a recurrent frontal pain are also often misdiagnosed as having chronic sinusitis.

Quality

Headache may be described as being:

- sudden in onset and explosive ('thunderclap headache');
- a tight internal pressure sensation as though the head were being inflated;
- external pressure like a weight on the head, a band around the head, or the head being held in a vice;
- intense, stabbing, or boring (cluster headache and TACs);
- throbbing (pulsatile).

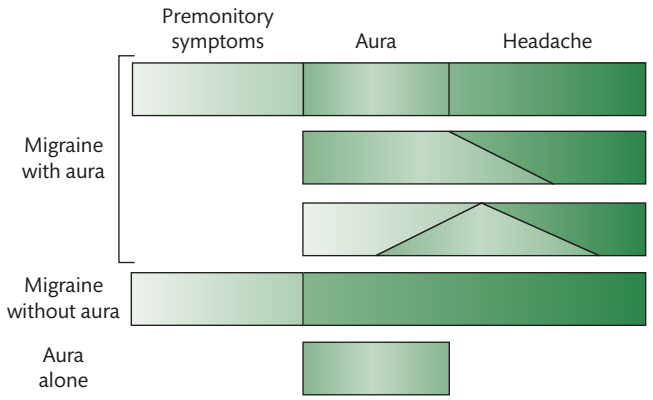

Figure 2.2 Classification of migraine syndromes according to the appearance of neurological symptoms (shaded areas) in relation to headache. Premonitory symptoms include changes in mood, alertness, and appetite that may precede migraine by a day or so.
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Beware of the patient's description of 'throbbing', which is often used to indicate severity or fluctuation in intensity rather than any relationship to the cardiac rhythm. Migraine may start as a dull constant headache but usually becomes pulsatile as severity increases.

'Ice cream headaches' from swallowing cold liquids or foods are commonly mid-frontal but may be referred to another part of the head if the sufferer is also subject to migraine that habitually affects that particular area.

Neuralgic pain is usually stabbing as in trigeminal neuralgia but is occasionally constant and burning as in some cases with occipital neuralgia.

Patients with chronic tension-type headache or migraine may also be subject to sudden jabs of pain in the head known as 'ice-pick pains'.

Associated features

Nausea and vomiting are common accompaniments of migraine. Sensitivity to light, sound, and smells is characteristic of migraine. Touching the scalp or skin may feel painful (allodynia) (2). The superficial temporal arteries may be seen to dilate and become tender to touch. It is as though the normal inhibitory control of afferent impulses from the special senses, skin, and blood vessels has been withdrawn as part of a 'nerve storm' (3).

Tension-type headache is notable for the absence of these distinctive features, although some patients do complain of a constant mild photophobia or occasional nausea.

Patients with cluster headache and the other TACs commonly experience cranial autonomic symptoms, including Horner's syndrome on the side affected by headache, and are commonly associated with redness and watering of the eye with blockage or running of fluid from the nostril on the affected side.

Headaches secondary to pathological conditions are more likely to be associated with more dramatic symptoms or signs. Neck rigidity is present in most, but not all, cases of subarachnoid haemorrhage, meningitis, or encephalitis. The sudden headache caused by a colloid cyst blocking the flow of cerebrospinal fluid (CSF) in the third ventricle may be accompanied by a 'drop attack'—sudden loss of power in the legs, without necessarily impairing consciousness because of a rapid increase in intracranial pressure. Patients may become drowsy, yawn, or vomit without preliminary nausea. Progressive dilatation of one pupil can be seen with a space-occupying lesion such as an extradural or subdural haematoma, causing tentorial herniation to compress the third cranial nerve, a signal for urgent action.

Skin rashes may be observed in childhood infections, septicaemia, and meningitis. Bony tenderness may be present over the forehead and cheeks in acute sinusitis even if there is no obvious nasal obstruction, and circumcorneal injection in glaucoma may also indicate the source of headache.

Precipitating or aggravating factors

The onset and nature of an aura may be determined by afferent input directed to a specific part of the cerebral cortex. For example, sunlight flickering through trees when driving along a tree-lined street or flashing lights in a disco can trigger a visual aura. One of our colleagues reported that holding a vibrating object such as the handle of a motor-powered lawn mower would induce tingling in that hand,

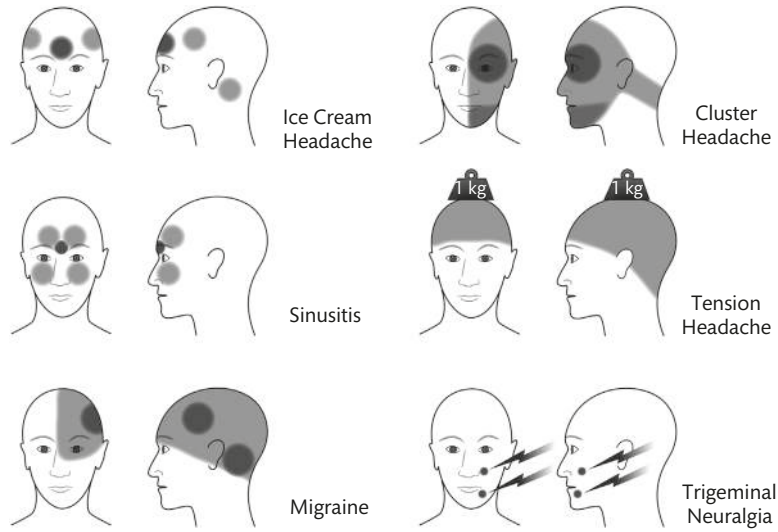

Figure 2.3 What part of the head aches? Regions commonly affected by six varieties of head pain are illustrated.
Reproduced from Lance JW, *Migraine and other headaches*, Simon & Schuster (Australia) Pty Limited. Copyright (1998) Lance JW.

spread up his limb on the affected side, and then develop into a fully blown sensory aura.

Common trigger factors include the following:

- Stress (migraine and tension-type headache). One patient developed a migrainous aura within minutes of receiving a threatening letter from a lawyer.
- Relaxation after stress (migraine), known as 'weekend headaches'.
- Phases of the menstrual cycle (premenstrual and mid-cycle when the blood oestradiol level drops in women).
- Excessive afferent stimuli (glare, flickering light, noise, and strong perfumes).
- Vasodilator drugs, alcohol (particularly cluster headache) or specific foods (migraine).
- Hypoglycaemia or dehydration.
- Excessive intake of tea or coffee (caffeine withdrawal headache).
- Exercise (exertional vascular headache).
- Sexual activity ('benign sex headaches', orgasmic headaches).
- Coughing (intracranial vascular headaches, 'benign cough headache', and raised intracranial pressure).
- Sustained neck posture or neck movements (upper cervical syndrome and tension-type headache).
- Talking, chewing, swallowing, touching the face, or feeling wind on the face (trigeminal neuralgia and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing).
- Change in sleep pattern, too little or oversleeping in the morning (migraine).
- Extreme weather changes (migraine and tension headache).
- Medications—exacerbation of headache may be caused by medications. It is important to determine if worsening of headache is temporally correlated with any new medications taken for other conditions, or change in the dosage of medications.

Patients with raised intracranial pressure or space-occupying lesions may complain that the headache is made worse by jolting or jarring of the head, sudden movements, coughing, or straining. Headache present on standing but eased by lying down suggests a state of low CSF pressure. Facial pain arising from the temporomandibular joints is made worse by chewing, jaw clenching, or grinding the teeth during sleep. Pain may develop in the temporal and masseter muscles ('claudication of the jaw muscles') when their blood supply is compromised by temporal arteritis.

Relieving factors

- During migraine headache the patient usually wishes to sit or lie quietly in a darkened room and finds benefit from sleeping, whereas a patient with cluster headache prefers to stand or pace the floor, holding one hand over the affected eye.
- Pressure on dilated scalp vessels and the use of hot or cold compresses are often soothing in migraine and cluster headache.
- Inhaling 100% oxygen through a mask at about 7 litres a minute relieves most patients with cluster headache.
- Relaxation of forehead and jaw muscles reduces the severity of tension-type headache.
- Tension-type headache is often relieved by drinking alcohol, in contrast to its adverse effect in migraine and cluster headache.
- Medications—the medications that provide relief from headache are often informative as to the nature of the headache.

Previous treatments

Any type of treatment tried previously should be listed, with a note about its success or failure. In recording medications used in acute treatment or prophylaxis it is important to ascertain the dosage where ever possible. Some patients may have been prescribed subtherapeutic doses, whereas others may have been consuming large amounts of analgesics without supervision.

Past health

Any illness associated with or preceding the onset of headaches should be listed together with any accident, injury, or operation.

Headaches may be a feature of infections, acquired immune deficiency syndrome (AIDS), malignancy, blood dyscrasias, vasculitis, polymyalgia rheumatica, and endocrine disorders. A system review for patients with headache should include eyes, ears, nose and throat, teeth, and neck.

Recurrent abdominal pain, vomiting attacks, and motion sickness in childhood are often precursors of migraine in later life.

A past history of asthma in a patient with migraine cautions against the use of beta blockers, which cause bronchoconstriction, in management.

If there is a past history of a thunderclap headache it is useful to enquire whether spinal root pains, in the buttocks and thighs some hours or days after the onset of headache, developed (as a pointer to blood tracking down the subarachnoid space to the cauda equina after haemorrhage).

Family history

More than half of migrainous patients have a positive family history. Twin studies have shown that approximately half of the susceptibility to migraine is of genetic origin and the other half is possibly determined by environmental influences. Familial hemiplegic migraine is inherited as a dominant gene. A positive family history for cluster headache has been reported to vary from 3% to 20%.

Personal background

It has been argued in legal circles that only factors of relevance should be included in a medical history. For any physician interested in headaches, any of the facts elicited in obtaining a detailed picture of each individual's personality, educational background, and lifestyle may prove to be relevant to his or her susceptibility to headaches. The following headings may prove useful:

- place of birth and cultural background;
- education (primary, secondary, or tertiary level achieved); when appropriate, the age of leaving school;
- occupational history;
- marital history, when appropriate;
- lifestyle;
- habits;
- extent of consumption of tea, coffee, caffeine-containing soft drinks, and alcohol, and the history of cigarette smoking, consumption of prescribed drugs, and the use of so-called 'recreational drugs';
- social life, involvement in community affairs;
- hobbies, recreations, and sports.

Unresolved problems may become apparent that could underlie chronic tension-type headache and the increasing frequency of migraine attacks. There may be financial or sexual problems, a sense of inadequate achievement, and other causes of resentment that may prove important in the psychological aspect of treatment. Some insight is usually gained into whether the patient's symptoms are exaggerated by loneliness and introspection, or whether they are being played down by somebody who has an active and interesting life.

Diagnosis based on the history

Onset of headache

The sudden onset of severe headache (thunderclap headache; see Chapter 34) may be the presentation of:

- subarachnoid haemorrhage;
- reversible segmental cerebral vasoconstriction (Call–Fleming Syndrome; see Chapter 49);
- sexual orgasm headache (which may be associated with the above form of cerebral vasospasm; see Chapter 25);
- meningitis, encephalitis (see Chapter 41);
- pressor responses as in patients with phaeochromocytoma, or ingestion of incompatible medications or tyramine-containing substances while on monoamine oxidase inhibitors;
- obstructive hydrocephalus (e.g. colloid cyst of the third ventricle);
- dissection of the carotid or vertebral arteries.

Subacute onset of headache

Possible causes include:

- an expanding intracranial lesion;
- progressive hydrocephalus;
- temporal arteritis in patients older than 55 years (see Chapter 46);
- idiopathic intracranial hypertension (see Chapter 39);
- intracranial hypotension (see Chapter 38).

Recurrent discrete episodes of headache or facial pain

- Migraine, including 'lower half headache' (facial migraine; see Chapter 6).
- Cluster headache (see Chapter 18).
- Trigeminal and other cranial neuralgias (see Chapter 27).
- Transient ischaemic attacks.
- Intermittent obstructive hydrocephalus.
- Paroxysmal hypertension.
- Tolosa–Hunt syndrome.
- Cough; exertional and benign sex headaches (see Chapter 25).
- Hypnic headaches (see Chapter 26).
- Ice cream headache
- Ice pick pains.
- Sinusitis as a cause of facial pain, rarely a cause of episodic headache (see Chapter 45).

Chronic headache or facial pain

- Tension-type headache (see Chapter 29).
- Chronic migraine (see Chapter 31).
- New daily persistent headache (see Chapter 30).
- Post-traumatic headache (see Chapter 35).

- Posterior idiopathic (atypical) facial pain (see Chapter 27).
- Postherpetic neuralgia.

Conclusion

Well, there it is then, a simple and logical approach that may enable a firm diagnosis to be made on the history alone. If not so, it should at least identify which patients require investigation to identify or eliminate a structural cause for the headaches. Along the way, it is hoped that we have got to know our patient better, avoid some tricks. and obtain some tips for treatment.

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3

Diagnostic neuroimaging in migraine

Mark C. Kruit and Arne May

Introduction

Migraine is a multiphasic disorder and understanding of its pathophysiology starts with the acknowledgement that migraine is not simply a disease of intermittently occurring pain, but that it involves processes that affect the brain over time (see Chapters 4 and 6). These processes seem to lead to increased sensitivity or hyperexcitability of different brain regions, facilitating paroxysmal headache and aura (1). Effects on the brain (structure, neurochemistry, function) and neurovascular system have been widely documented during the different phases of migraine, and neuroimaging has played a significant role in the current understanding of the pathophysiological processes behind migraine. However, these processes are still only partially understood, are likely multifactorial, and involve several brain structures.

The pathophysiological mechanism behind migraine aura symptoms is cortical spreading depression (CSD; see Chapter 4). This is a transient activation followed by depression of activity in neural tissue, which slowly propagates in brain tissue (2, 3). CSD most often involves the occipital lobe, leading to visual symptoms in about 30% of patients. During CSD regional brain hyper- and hypoperfusion reductions of blood–brain barrier integrity and plasma extravasation have been described (see subsection 'Neuroimaging findings in (prolonged) aura').

Neuroimaging has contributed significantly to the current neuroscientific knowledge of structural and functional brain changes during the ictal phase (aura and headache) of migraine (4–6). It is, however, largely unknown which parts of the brain structurally, functionally, or biochemically change earlier on, during the premonitory phase (7). The thalamus, hypothalamus, and probably other deep brain and brainstem structures seem to play a role. Further research focusing on such early changes in the premonitory phase may provide insight into when and why brainstem nuclei and pain networks become paroxysmally dysfunctional, how the trigeminovascular system becomes activated, and what pathophysiological changes precede and characterize the aura symptoms. Given the diagnostic focus of this chapter, the neuroscientific neuroimaging findings (based on, e.g., voxel-based morphometry, diffusion tensor imaging, magnetic resonance spectroscopy, etc.) underlying migraine pathophysiology are considered out of scope here, and will therefore not be discussed further.

Diagnostic neuroimaging indications in migraine

The diagnosis of primary headaches is primarily a clinical task, based on history-taking and careful neurological examination. No single instrumental examination has yet been able to define or ensure the correct diagnosis, or to differentiate idiopathic headache syndromes. However, it is common knowledge that some patients with migraine display irregularities on Doppler ultrasound of cranial vessels, abnormalities in electroencephalography readings between and during attacks, and occasionally unspecific white matter changes on magnetic resonance imaging (MRI). These white matter changes have been linked with an increased risk of brain lesions in patients with migraine. Although the interpretation of finding such white matter changes in individual patients with migraine is clinically challenging, given that functional correlates are completely lacking, it may be that they are a markers that indicate risk factors for future stroke or for the development of chronic headache. Longitudinal studies are certainly crucial in assessing whether these lesions are progressive and need the attention of clinicians.

In cases of *acute headache* (like primary thunderclap headache or after trauma, etc.) or suspected symptomatic headache, the need for neuroimaging is clearly evident, and will not be discussed further in this chapter. For *non-acute headache*, as applies to most migraine patients, neuroimaging is overused and is only in selected cases considered to be appropriate.

Computed tomography (CT) and MRI scans are frequently requested and performed in migraine patients who seek medical help. Often this is driven by the patient's anxiety about having an underlying pathological condition, or to improve the patient's overall satisfaction and medical care. The fact that radiological examinations are not particularly invasive or uncomfortable reduces thresholds further. In selected patients, like those with chronic daily headache with anxiety disorders, it has been shown that neuroimaging reassures patients effectively and significantly reduces costs, possibly by changing the subsequent referral patterns of the general practitioner (8).

However, particularly in patients presenting with typical primary headaches, the very low likelihood of detecting explanatory underlying diseases that change treatment or diagnosis must be considered. Combined results of imaging studies (CT and MRI) in over 3700 headache patients (not exclusively 'typical migraine') together

shows a low yield of about 0.4% in those with migraine (9–11). In patients with 'typical migraine', the yield is likely to be even lower.

A potential risk of unnecessary imaging is the discovery of an incidental finding, which eventually needs further diagnostic work-up or follow-up. Further potential problems include false-positive studies, false reassurance from an inadequate study, allergic reaction to contrast agent, and so on (12). Furthermore, the current resource-restricted medical environment requires more and more evidence-based justification for diagnostic imaging.

American Academy of Neurology recommendations

In 2000, the quality standards subcommittee of the American Academy of Neurology (AAN) published an evidence-based guideline on the role of neuroimaging in patients with headache to assist physicians in making appropriate choices in diagnostic work-ups (13). A total of 28 studies (from 1966 to 1998) were reviewed. Based on reported rates of 'abnormalities related to headache that may require further action' (e.g. acute cerebral infarct, neoplastic disease, hydrocephalus, aneurysm, or arteriovenous malformation) combined with data from patient history and neurological examination, the following symptoms were identified to increase significantly the odds of finding a significant abnormality on neuroimaging in patients with non-acute headache (13):

- rapidly increasing headache frequency;
- history of lack of coordination;
- history of localized neurological signs or a history such as subjective numbness or tingling;
- history of headache causing awakening from sleep (although this can occur with migraine and cluster headache).

Based on these findings, the following AAN recommendations for non-acute headache were formulated:

- consider neuroimaging in patients with an unexplained abnormal finding on the neurological examination (grade B);
- consider neuroimaging in patients with atypical headache features or headaches that do not fulfil the strict definition of migraine or other primary headache disorder (or have some additional risk factor, such as immune deficiency), when a lower threshold for neuroimaging may be applied (grade C);
- neuroimaging is not usually warranted in patients with migraine and a normal neurological examination (grade B).

European Federation of Neurological Societies guidelines

The European Federation of Neurological Societies (EFNS) published a similar guideline for the management of non-acute headache (revision in 2010) (14), which was also mainly based on a review of published evidence (9, 10). The EFNS guideline includes the following summarized statements relevant for migraine (grade B recommendations):

- in adult and paediatric patients with migraine, with no recent change in pattern, no history of seizures, and no other focal neurological signs or symptoms, the routine use of neuroimaging is not warranted;
- exceptions to this rule should be made in the diagnosis of trigeminal autonomic headaches and headaches that are aggravated by exertion or a Valsalva-like manoeuvre (11);
- in patients with atypical headache patterns, a history of seizures, or neurological signs or symptoms, or symptomatic illness such as tumours, AIDS, and neurofibromatosis, MRI may be indicated;
- when neuroimaging is warranted, the most sensitive method should be used, and MRI (not CT) is recommended in these cases;
- with a normal unenhanced MRI, in the absence of other disease and suspicion on metastasis/vasculitis/etc., there is no need for additional scanning with gadolinium;
- there is no role for conventional Röntgen techniques;
- digital subtraction angiography is not appropriate in the screening of patients with headache for intracranial disease.

Summarized recommendations

In the recent meta-analysis by Detsky et al. (11), data from more than 3700 patients were included. The recommendations from this meta-analysis are consistent with the AAN and EFNS guidelines, although additional recommendations were included to perform imaging in cases with (i) non-visual aura (sensory or motor); (ii) an aura that has changed in character; or (iii) an aura that cannot be clearly described as typical of migraine aura.

Since a 2007 case series demonstrated that even cluster headache with a typical time pattern and an excellent response to typical treatment can still be caused by underlying structural pathology such as a pituitary tumour, patients with trigeminal autonomic headaches should be considered for neuroimaging (15).

No evidence exists that elderly patients who experience headache, but have normal findings in a neurological examination, should undergo neuroimaging. However, when patients who are older than 50 years present with a first or a new type of headache, neuroimaging may be considered.

In summary, patient history, details of symptoms, and careful clinical neurological examination are together the most important tools in diagnosing and treating migraine. In most patients with non-acute headache this will lead to a reliable diagnosis (applying the International Classification of Headache Disorders (ICHD) criteria) and do not require any further laboratory tests or neuroimaging. While positron emission tomography and functional MRI are of little or no value in the typical clinical setting of primary headaches, they are believed to have vast potential to aid exploration of the pathophysiology of headaches and the effects of pharmacological treatment.

Box 3.1 summarizes the combined recommendations on the use of neuroimaging in patients with non-acute headache.

Migraine and stroke

Accumulating evidence from the last three or four decades has expanded the spectrum of neurovascular pathology linked to migraine (see also Chapters 10 and 37). Initial case reports of 'migrainous stroke' were followed by retrospective and prospective, mostly hospital-based, case–control studies assessing the prevalence of clinical ischaemic and haemorrhagic stroke in migraine patients, showing a consistent association between migraine with aura and stroke; the association with migraine without aura is less evident (16,17). MRI studies have further identified that migraine is also associated with markers of small vessel disease, including (progressive) white matter lesions (WMLs), brainstem T2 hyperintensities,

Box 3.1 Recommendation on the use of diagnostic neuroimaging in non-acute headache

- **A** Consider neuroimaging in non-acute headache patients with 'red flags':
  - unexplained abnormal findings on neurological examination;
  - (atypical) headaches that do not fulfil ICHD-2 criteria for primary headaches;
  - additional risk factors (e.g. immune deficiency, tumours, etc.);
  - history of (associated) seizures;
  - recent changes in headache pattern;
  - non-visual (e.g. sensory or motor) or atypical aura pattern.
- **B** Neuroimaging in not usually warranted in patients with typical migraine with or without aura and normal neurological examination.
- **C** When neuroimaging is warranted, magnetic resonance imaging is the primary method of choice.

Box 3.2 Diagnostic criteria for migrainous infarction

- **A** A migraine attack fulfilling criteria B and C.
- **B** Occurring in a patient with 1.2 *Migraine with aura* and typical of previous attacks except that one or more aura symptoms persists for >60 minutes.[1]
- **C** Neuroimaging demonstrates ischaemic infarction in a relevant area.
- **D** Not better accounted for by another ICHD-3 diagnosis.

[1] There may be additional symptoms attributable to the infarction.

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posterior circulation subclinical infarcts, and microbleeds (18–20). And, finally, reports from epidemiological studies on associations between migraine and coronary events (21,22) and all-cause mortality (23) further illustrate the broad spectrum of lesions associated with migraine, likely to be explained via complex relationships (24).

The relationship between migraine and stroke is complex, and the following paragraphs will expand on different aspects of this relationship; neuroimaging examples will illustrate how migraine patients with (suspicion of) haemorrhagic or ischaemic stroke may present.

Firstly, migrainous infarction and its imaging appearances will be described, followed by a section on 'aura-related' neuroimaging findings, because the clinical symptoms of either 'infarction' or 'aura' are often very similar in the acute and sub-acute moments of presentation.

Migrainous infarction

Kurth et al. (24) suggested that the first report on migrainous infarction was probably by Féré (25), who, in 1883, described a patient with migraine who died after 2 months of headache, visual disturbances, and hemiplegia. Various case reports of migrainous infarction have been published since then, and have made clear that migraine can act as a direct cause of ischaemic stroke. In such cases stroke is assumed to be directly and causally related to an acute migraine attack.

Because it is often impossible by clinical examination alone to differentiate between transient ischaemic attack, prolonged aura, and migrainous infarction, MRI (notably with diffusion weighting) today plays a key role in the diagnosis of migrainous infarction. The current ICHD-III criteria strictly define *migrainous infarction* as ischaemic stroke that occurs when, during a typical migraine with aura attack, one or more migrainous aura symptoms persist longer than 60 minutes, with neuroimaging proof of an associated ischaemic brain lesion in an appropriate region, and absence of other underlying causes (see **Box 3.2**) (27).

Based on this definition, it is indirectly evident that migraine patients who present with 'prolonged aura symptoms' require an appropriate neuroimaging work-up with MRI and, when an acute ischaemic lesion is present, additional diagnostic work-up to exclude other underlying disorders. In cases of co-existing other causes (e.g. cardiac arrhythmia, coagulation disorders, embolism through a patent foramen ovale, cervical artery dissection), the diagnosis then has to be (changed to) *ischaemic stroke co-existing with migraine*. The same applies when in a patient with a history of migraine without aura, an ischaemic lesion develops during or after a migraine attack. In other cases, when criteria are not completely fulfilled, ischaemic stroke in a patient with migraine may be categorized as *cerebral infarction of other cause presenting with symptoms resembling migraine with aura* (26).

In past decades, the diagnostic criteria for migrainous infarction have been changed (ICHD-1 vs ICHD-2) and studies inconsistently applied the criteria. This probably explains the relatively wide range (0.8–3.4 per 100,000) of reported annual incidences (28–31), and points at a probable amount of overdiagnosis (32). Although this implies that migrainous infarction is a rare condition, which is further illustrated by Wolf et al. (33), who estimated that it accounts for approximately 2 in 1000 'overall' strokes per year, it needs to be considered that migrainous infarction predominantly affects younger patients. In that age category migrainous infarction was estimated to account for 13% of first-ever ischaemic strokes (34).

Neuroimaging findings in migrainous infarction

The largest series of migrainous infarction cases to date have been reported by Wolf et al. (17 cases)(33) and Laurell et al. (33 cases) (33,35). In both reports patients underwent an appropriate stroke work-up, and were diagnosed according to ICHD-2 criteria (**Table 3.1**) shows the main findings of the studies.

Both studies reported a clear predominance of infarcts in the posterior circulation, supporting previous observations. The low age at stroke onset is a further key finding in both studies; therefore, when treating a young patient presenting with stroke, migrainous infarction should be kept in mind. In both studies, outcome was relatively favourable. Although no studies have systematically examined the appearance of migrainous infarcts, from a number of case reports it is suggested that the ischaemic insults predominantly affect the cortex when supratentorial. Similarly, cortical ischaemia that crosses different vascular territories may also point to a migrainous infarct mechanism, but this is probably an infrequent finding, as in the study by Wolf et al. (33) no such 'crossing' lesions were identified, neither on diffusion-weighted imaging (DWI) nor on perfusion-weighted imaging (PWI). However, aura-related hypoperfusion typically seems to cross territories.

The underlying mechanisms of migrainous infarction are unknown but are probably related to CSD-related changes, including hypoperfusion and changes in blood–brain barrier permeability (which might lead to an exacerbation of local cellular injury caused

Table 3.1 Recent case series of migrainous infarction

	Laurell et al. (34)	Wolf et al. (32)
Cases	n = 33 (all ICHD-2)	n = 17 (n = 11 ICHD-2)*
M:F (%)	39:61	23:77
Age at stroke onset (y)	19–76, median 39	20–71, mean 45
Posterior circulation (%)	82	71
Cerebellum (%)	21	6
Multiple lesions (%)		41
Family history of migraine (%)	75	24
Patent foramen ovale (%)	40	65

* n = 6 had a history of migraine without aura (thus not fulfilling the ICHD-2 criteria in the strict sense) and presented with first-ever neurological symptoms compatible with migraine with aura and concomitant migraine headaches.

by ischaemia). Together with factors predisposing to coagulopathy and release of vasoactive neuropeptides, further changes in cerebral haemodynamics, arterial thrombosis, and infarctions may be explained (19).

In Figures 3.1–3.4 case descriptions illustrate various presentations and appearances of migrainous infarcts. In Figure 3.5 a case with 'Cerebral infarction presenting with symptoms resembling migraine with aura' is described, and illustrates that it can be difficult to apply a correct and meaningful diagnosis, given the strict ICHD-2 criteria.

Neuroimaging findings in (prolonged) aura

According to the ICHD-2 criteria, a diagnosis of persistent aura without infarct can be applied when aura symptoms remain present for longer than 1 week and when there is no neuroradiological evidence of ischaemia. This is a rare condition that seems to affect genetic forms of migraine (such as familial hemiplegic migraine) somewhat more often.

Incidentally, in 'regular' migraine with aura patients, aura symptoms also persist for longer than 60 minutes. When more than one

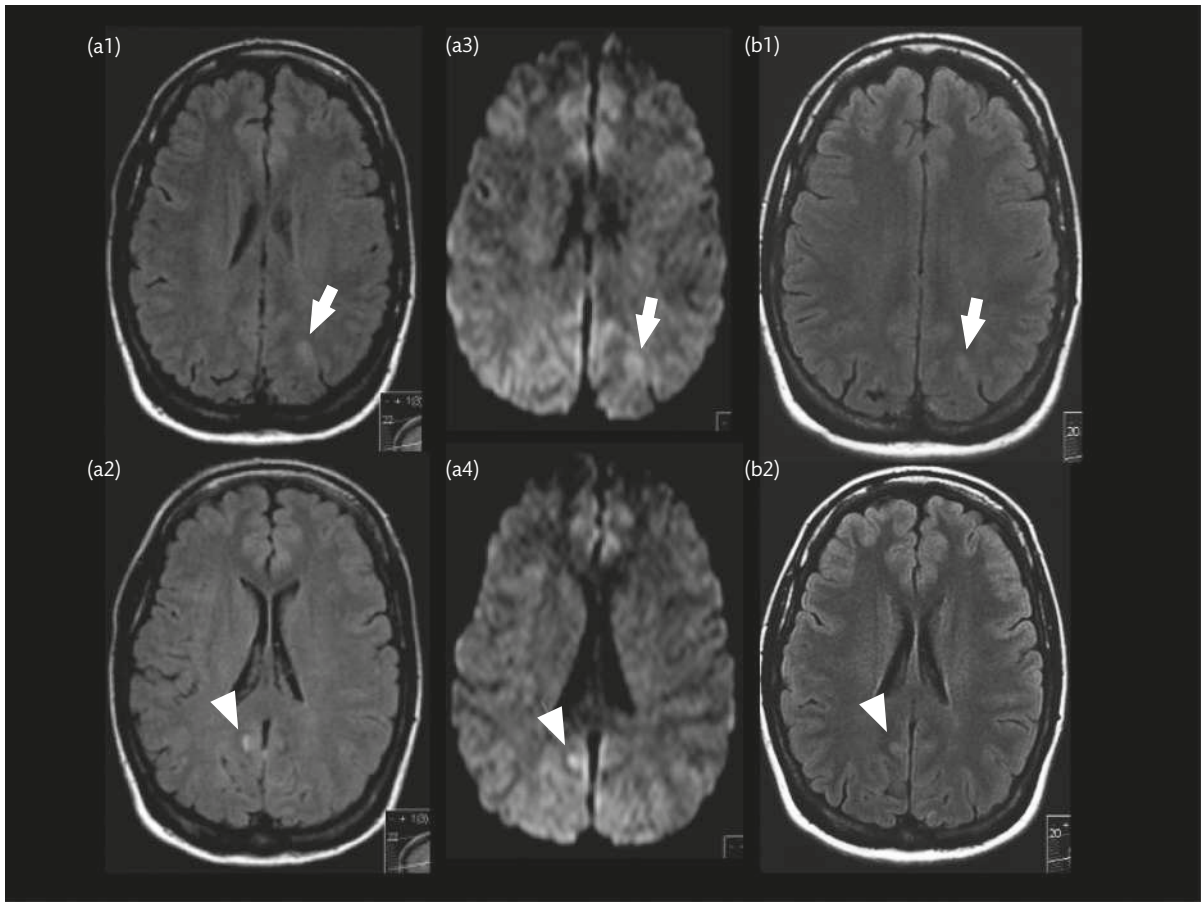

Figure 3.1 Bilateral occipital migrainous infarction.

A 33-year-old woman with migraine without aura since childhood, and also, since the age of 21, attacks with visual aura. She presented with the usual visual aura symptoms but now has a persisting visual field defect, and persisting positive scintillating scotoma, accompanied by migraine headache. There were no other neurological signs or symptoms. Family history for migraine with aura was positive. A magnetic resonance imaging (MRI) scan performed after 1 day of symptoms revealed, bilaterally in the occipital lobe, small cortical areas of diffusion restriction. There were no other abnormalities. Computed tomography angiography of the cervical and intracranial arteries was negative (not shown). There were no other underlying causes. Follow-up MRI after 3 weeks showed only minimal residual hyperintensity on the fluid-attenuated inversion recovery (FLAIR) images, consistent with near normalization of the ischaemic foci. Images: (a1) and (a2) FLAIR images; (a3) and (a4) corresponding B1000 diffusion-weighted images in the acute setting; (b1) and (b2) FLAIR images after 3 weeks of follow-up.

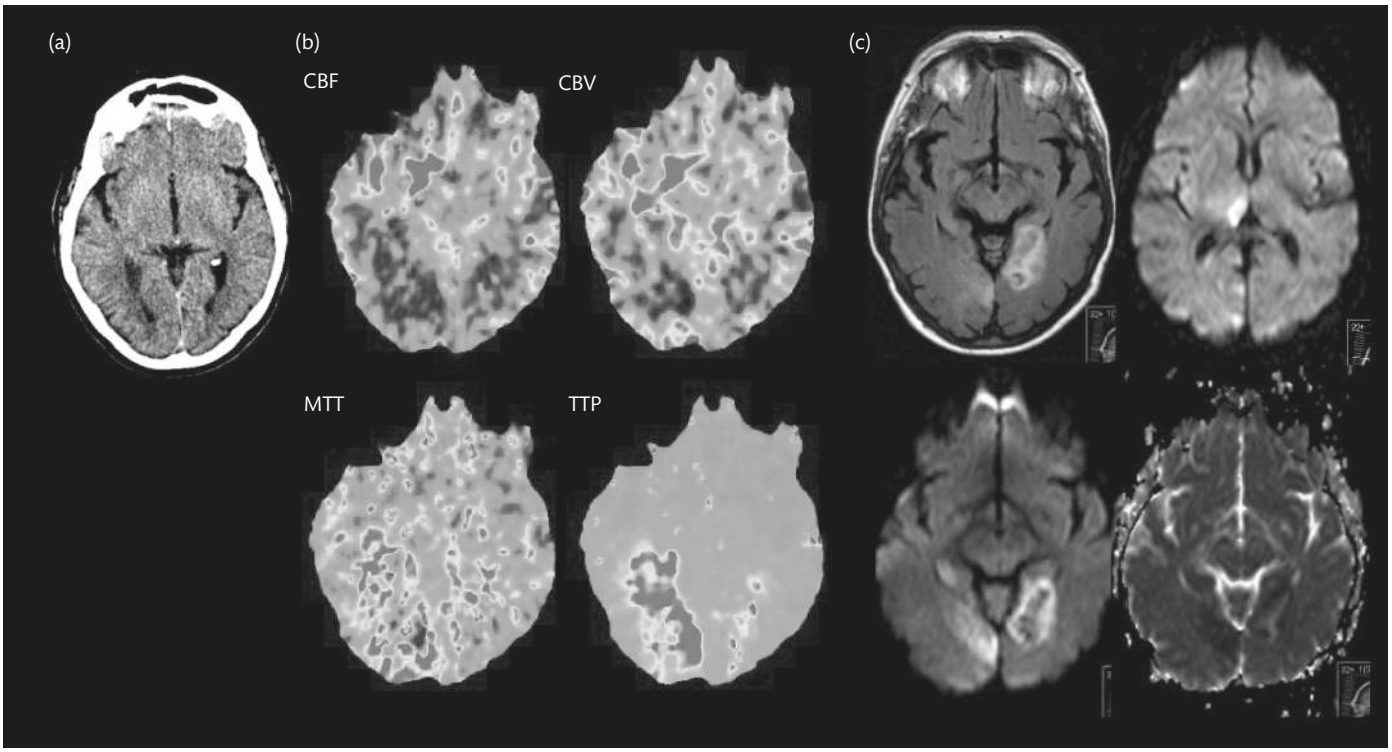

Figure 3.2 (see Colour Plate section) Bilateral occipital and thalamic migrainous infarction.

A 61-year-old woman with a long history of migraine with aura presented with a persisting left upper quadrant visual field defect that had developed during a regular migraine with visual aura attack. (a) Initial non-contrast computed tomography (CT) dubiously showed some reduced grey–white matter differentiation in the right occipital lobe. CT angiography (not shown) showed normal calibre of the carotids, the vertebrobasilar system, and the posterior cerebral arteries; the posterior communicating arteries were not identified. (b) Whole-brain perfusion CT demonstrated reduced cerebral blood volume (CBV) and cerebral blood flow (CBF), and prolonged mean transit time (MTT) and time to peak (TTP) values in the right occipital lobe, but also to a lesser degree in the left occipital lobe. (c) Magnetic resonance imaging after 1 day confirmed recent bilateral infarction, with signs of haemorrhagic transformation on the left side (arrowhead), but also identified right-sided thalamic infarction. In the following diagnostic work-up, no other underlying causes were identified.

aura symptom is present (e.g. visual and sensory symptoms together or in succession), for each type 60 minutes may be accepted. When aura persists for longer, this might point to migrainous infarction, although most often the symptoms spontaneously normalize, and patients will probably only be scanned incidentally. By definition, imaging studies in such 'non-infarct' cases do not show ischaemic changes, but various case reports and series have described other CSD- or aura-related effects on the brain tissue and neurovascular system, which will be discussed in the following paragraphs.

Cutrer et al. (36) and Sanchez del Rio et al. (37) studied spontaneous migraine episodes with perfusion-weighted MRI, including six patients studied during regular (not-prolonged) visual aura, within 31 ± 6 minutes after the onset of visual symptoms. In all studies perfusion deficits were observed in the occipital visual cortex from which the hemifield defect was originating. Maximum measured changes were a 37% decrease in cerebral blood flow (CBF), a 33% decrease in relative cerebral blood volume, and an 82% increase in mean transit time (MTT). Several small series and case reports have been published since then, mostly with consistent findings of mild regional hypoperfusion, uni- or bilaterally affecting overlapping vascular territories.

Förster et al. (38) reported a prospective study in which patients with suspected acute ischaemic stroke were evaluated. In this study, 33 patients with a final diagnosis of migraine with aura were compared with age-matched patients with a final diagnosis of acute ischaemic stroke. As a consequence of the study methodology, in this cohort the number of patients with 'rare' aura symptoms (like hemihypaesthesia, hemiparesis, and aphasia) was over-represented, as well as 'acute onset' of symptoms. In 54% (n = 18) of migraine with aura PWI showed hypoperfusion, which involved more than the posterior cerebral artery (PCA) territory in all but one of the patients, although the PCA territory was predominantly involved in 61% of cases. In seven patients (39%) the hypoperfusion extended to the parietal, temporal, or frontal lobe. There was no clear association between clinical symptoms and location of perfusion changes. There were no DWI abnormalities related to the aura symptoms, and there were no vessel occlusions or stenoses on magnetic resonance angiography (MRA). In comparison with acute ischemic stroke patients, the aura patients more often had hypoperfusion involving more than one territory, and less increased time to peak and MTT ratios. Figure 3.6 (from the original publication by Förster et al. (38)) illustrates a typical 'prolonged aura' case with parieto-occipital hypoperfusion without diffusion abnormalities, and with subtle dilation of the regional vasculature on MRA.

A few reports pointed to the occurrence of 'crossed cerebellar diaschisis' in cases with aura-related perfusion changes. Dodick and Roarke (39) reported a migraine patient with typical attacks of sensory aura for 30–60 minutes followed by headache, who showed

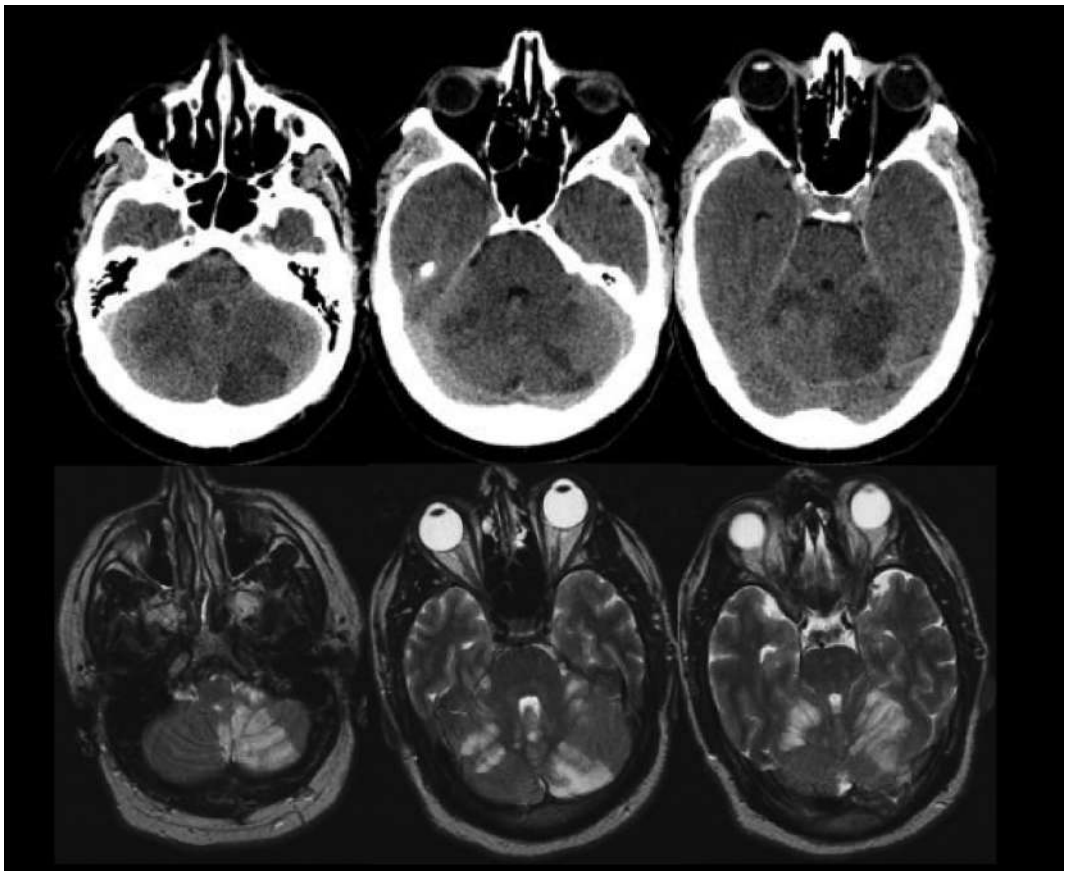

Figure 3.3 Bilateral cerebellar migrainous infarction.

A 45-year-old man with migraine with aura, who had visual aura attacks since the age of 35, with an average attack frequency of two per year, presented with the usual visual aura symptoms, which had lasted longer than normal and were accompanied by sensory symptoms over his whole body, and diplopia and dysarthria. Non-enhanced computed tomography (upper row) was performed after a few hours, and showed bilateral cerebellar hypodensities consistent with bilateral cerebellar infarction. A subsequent magnetic resonance imaging scan (T2 images, lower row) confirmed the presence of three cerebellar and one vermian infarct. Magnetic resonance angiography of the cervical and intracranial arteries was negative (not shown). No other underlying causes were found.

reversible reduction in CBF in the left cerebral hemisphere and associated crossed-cerebellar diaschisis (hypoperfusion in the right cerebellar hemisphere) during a typical attack on a brain single-photon emission CT (SPECT) scan. Iizuka et al. (40,41) observed in a case with prolonged aura crossed cerebellar hyperperfusion on brain SPECT scan on day 2 after symptom onset, which was explained as a consequence of uncoupled hyperperfusion with low function in the left cerebral hemisphere (corresponding to the neurological deficits). Both the crossed hyperperfusion and hypoperfusion illustrates the possibility of associated flow (and metabolic) alterations distant to and opposite of the primary site of disturbances, which could be relevant in understanding the occurrence of silent ischaemic lesions in the cerebellum in migraine patients (see later).

Besides flow alterations, a variety of other imaging findings have been described on brain imaging during (prolonged) migraine aura, which together may be explained by temporary changes in blood–brain barrier function, which are probably secondary to aura-related CSD and/or spreading hypoperfusion. A number of reports described 'vasogenic leakage', which may present as regional sulcal hyperintensity on native fluid-attentuated inversion recovery (FLAIR) MRI images (42) as (delayed) subarachnoid (sulcal), leptomeningeal, or cortical gadolinium enhancement on FLAIR or T1-weighted MRI scans (40,41,43,44), or as increased vascular permeability on perfusion-weighted MRI (45). In a few cases with (prolonged) aura, symptoms may be associated with reversible cortical swelling and hyperintense signal changes on FLAIR images, distributed along the regional cortical ribbon corresponding to the symptoms, without clear diffusion restriction (vasogenic oedema) (46). Figure 3.7 provides an examples of 'increased vasogenic leakage' as presented in the literature.

Migraine as a risk factor for clinical ischaemic stroke

Besides the (rare) presentation of 'migrainous infarction' (i.e. directly related to a migraine attack), migraine patients also have a higher chance of presenting with an ischaemic or haemorrhagic stroke unrelated to a migraine attack.

Over the past four decades, many observational studies, hospital-based stroke case–control studies, and population-based studies have evaluated the association between migraine and clinical

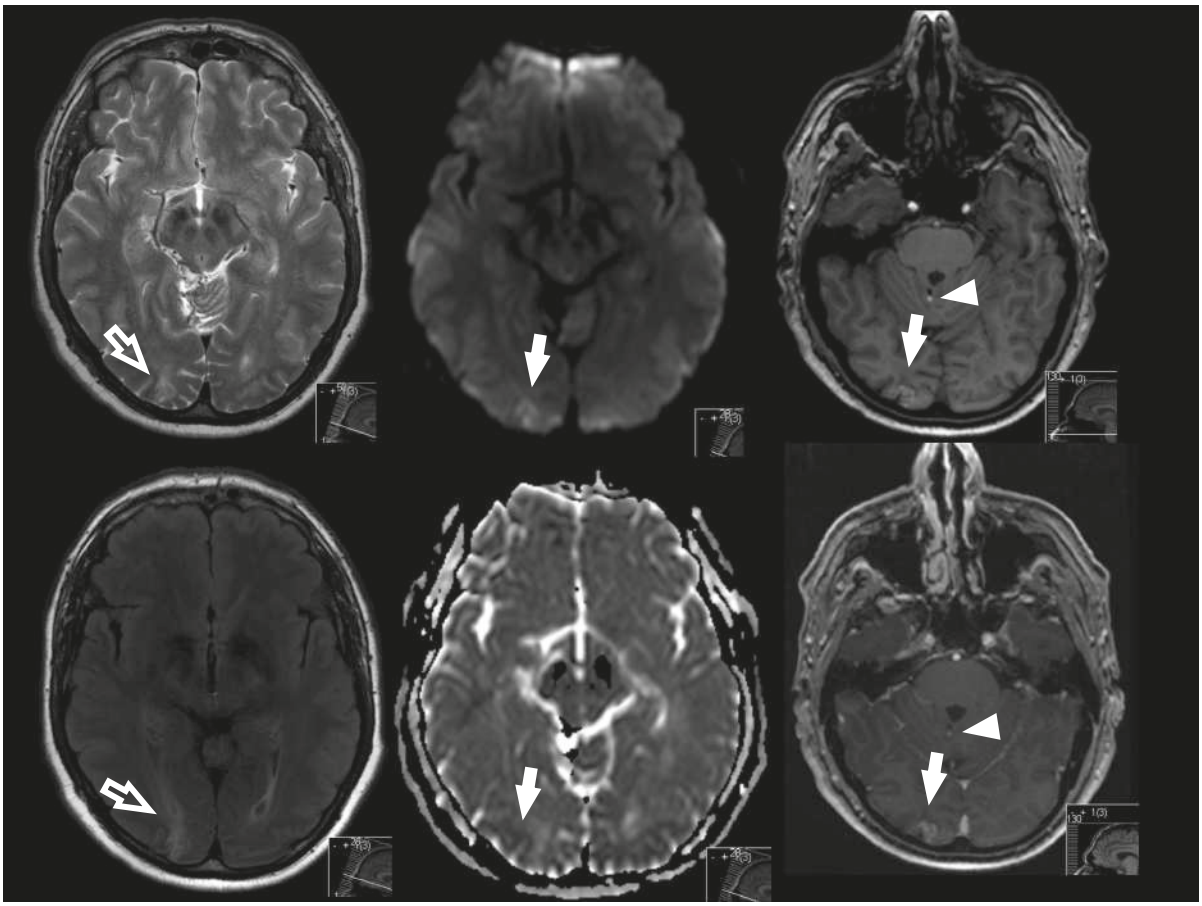

Figure 3.4 Subacute right occipital migrainous infarct.

A 58-year-old man with migraine with aura, with visual and sometimes sensory aura attacks since childhood, presented with a history of recent persisting visual aura symptoms for >1 week, followed by partial spontaneous recovery. Magnetic resonance imaging was performed to exclude ischaemia or other underlying causes. The scan was performed 12 days after the start symptoms, and showed a subacute occipital corticosubcortical infarct on the right: hyperintensity on FLAIR and T2 slices (open arrows); cortical diffusion restriction and signs of cortical necrosis (arrows). Note a small lipoma in the vermis, initially diagnosed as suspicious for an arteriovenous malformation (arrowhead).

ischaemic stroke. Meta-analyses of these studies revealed that migraine patients are about at doubly increased risk (16,47,48), which notably applies to patients with migraine with aura. Schürks et al. (16) calculated a pooled relative risk of 1.7 (95% confidence interval (CI) 1.3–2.3) for migraineurs versus controls (16). Data specified by migraine subtype were available from eight studies, resulting in a pooled relative risk of 2.2 (95% CI 1.5–3.0) for patients with migraine with aura and 1.2 (95% CI 0.9–1.7) for patients with migraine without aura versus controls. A higher migraine frequency seems also to further increase the risk of ischaemic stroke (49,50). Owing to the lower prevalence of migraine in men, the association between migraine and ischaemic stroke is less certain in men.

The risk is highest in women, notably at younger age (<45 years), and in this group the risk further increases (up to 10 times increased risk) with concurrent use of oral contraceptives. In individual studies the effects of concurrent hypertension and heavy smoking showed a greater than multiplicative effect on risk (51,52). Associations with markers of endothelial dysfunction and factors linked to prothrombotic or pro-inflammatory conditions have also been suggested as explanatory for the increased stroke risk in migraine (53). Genetic factors, including polymorphisms in *MTHFR, ACE, MEPE*, and *IRX4*, g have been linked with both migraine and ischaemic stroke, but further studies are needed to assess the pathophysiological relevance of such findings.

Topographical and pathophysiological considerations

Few structured data exist on the topography of non-migrainous infarcts in migraine patients. In a large series of 3500 patients with acute stroke, 130 (3.7%) had active migraine, and about 50% of these were <45 years of age. In the younger patients, posterior circulation involvement (55%) was characteristic (54). From case reports and small series is was also suggested that the occipital lobe and/or the posterior cerebral artery territory seem to be over-represented in migraine patients with clinical ischaemic stroke (55). Øygarden et al. (56) retrospectively investigated whether the lesion pattern on DWI MRI scans was different between migraineurs (with and without aura; n = 196) and non-migraineurs (n = 720) with clinical ischaemic stroke. In the migraine group, younger patients and women were over-represented, and infarcts were more often due to cardio-embolism and less often due to small vessel disease, than in the control group. Migraine patients presented more often with symptoms from the posterior circulation and had more cortical (odds ratio (OR) 1.8, 95% CI 1.3–2.5), small (OR 1.9, 95% CI 1.04–3.5), cerebellar (P = 0.026),

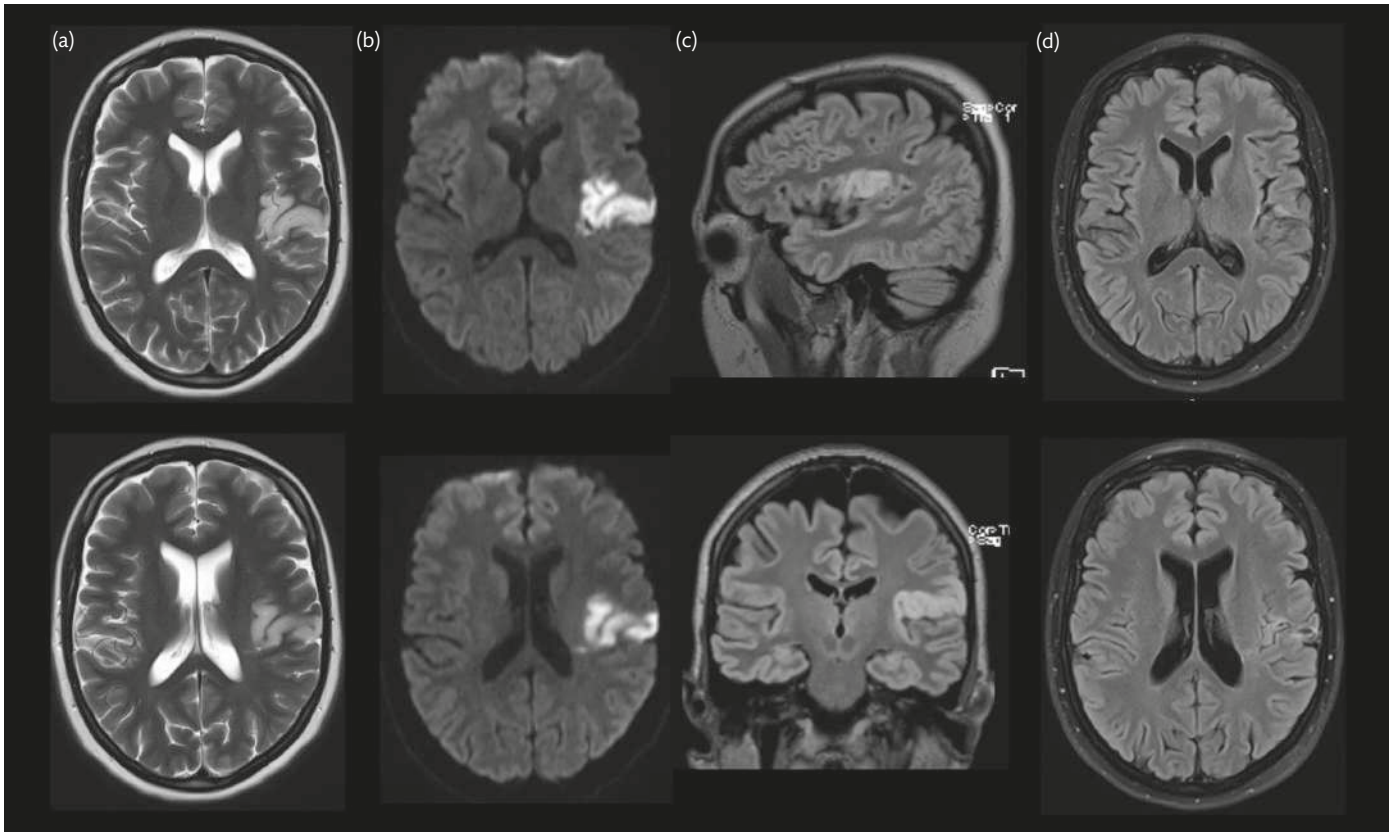

Figure 3.5 Cerebral infarction presenting with symptoms resembling migraine with aura.

A 46-year-old woman with migraine with aura, with regular attacks of (left-sided) visual aura since the age of 22, woke up in the morning with right-sided hemiparesis and aphasia, with associated migraine-like headache, which was followed in the hospital by a unilateral pulsating headache with nausea and vomiting, resembling her prior migraine attacks. The non-contrast computed tomography scan in the acute setting showed slight hypodensity (not shown). A magnetic resonance imaging (MRI) scan 1 day later confirmed a cortically restricted zone of cytotoxic oedema in the left middle cerebral artery (MCA) territory involving parts of the frontoparietal and insular cortex, consistent with her symptoms ((a) T2-weighted images; (b) B1000 diffusion-weighted images; (c) sagittal and coronal fluid-attenuated inversion recovery (FLAIR) images). Additional diagnostic work-up remained negative for other underlying causes. The patient recovered completely, although a follow-up MRI scan after 1 year ((d) FLAIR images) showed postischaemic cortical parenchymal loss. The cortically restricted infarct was considered somewhat unusual for ordinary MCA stroke and might have been due to aura-related cortical spreading depression. However, because the infarction was not clearly temporally related to a migraine with aura attack that was similar to previous attacks, the diagnosis was 'Cerebral infarction presenting with symptoms resembling migraine with aura', and not 'migrainous infarction'.

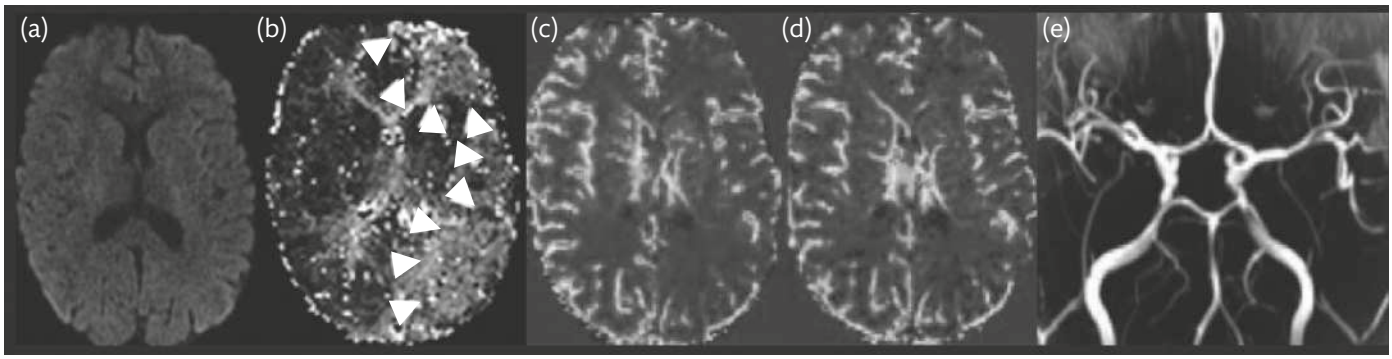

Figure 3.6 (see Colour Plate section) Regional hypoperfusion in prolonged aura.

Example of multimodal magnetic resonance imaging in migraine aura. (a) Diffusion-weighted imaging is unremarkable, while (b–d) perfusion maps (time to peak, cerebral blood flow, cerebral blood volume) demonstrate an extensive hypoperfusion in the left frontal, parietal and occipital lobes. (e) Magnetic resonance angiography demonstrates subtle dilation of the left middle cerebral artery branches.

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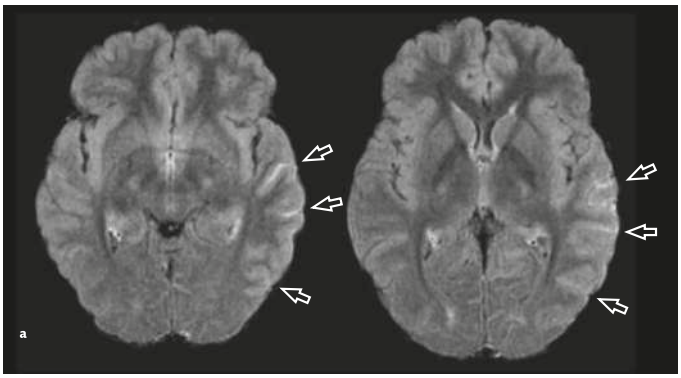

Figure 3.7 Reversible disturbed blood–brain barrier in (prolonged) aura

Fluid-attenuated inversion recovery images acquired 10 hours after onset of sensory aura symptoms (numbness around the lips on the right side of the face that spread to the right hand within 5 minutes and lasted for more than 1 hour) in a 22-year-old woman with a history of migraine without aura. Images show (arrows) linear hyperintensity in several parietotemporal sulci, without signal changes in the underlying parenchyma. There were no diffusion- or perfusion-weighted imaging abnormalities and there was no gadolinium enhancement (not shown). A lumbar puncture ruled out a subarachnoid haemorrhage; cerebrospinal fluid was normal. Follow-up after 4 days showed normalization of the magnetic resonance imaging scan (not shown).

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and occipital infarcts (13.3% vs 8.6%; $P = 0.05$). Migraine patients with infarcts had a three-times-higher chance of having a patent foramen ovale.

Øygarden et al. (56) suggested that the higher frequency of smaller lesions in migraineurs with aura may point at a higher vulnerability to damage following minor ischaemic insults (as was similarly described in experiments in mice with familial hemiplegic migraine) (57), or that ischaemia in migraineurs may simultaneously lead to a small, 'clinically silent' ischaemic lesion (that normally would not be noticed) and ischaemia-triggered CSD resulting in 'clinical' stroke-like neurological deficits leading to hospital admission (56).

Although the earlier study results were criticized (e.g. because of potential misclassification, referral bias, lack of neuro-imaging proof, etc.), the consistent findings in several studies over the years have migraine set today as an acknowledged ischaemic stroke risk factor. It has to be noted that in absolute terms stroke in young women with migraine (estimated at 5.5/100.000 annually) (58) remains rare, although at the same time, in this age group migraine should be considered an important risk factor.

Migraine as a risk factor for clinical haemorrhagic stroke

Data on a possible association between migraine and haemorrhagic stroke have remained inconsistent for years. However, in 2013, Sacco et al. (17) meta-analysed a total of four case–control (59–61) and four cohort studies (62–65) that together included 320,539 individuals in whom 1600 intracerebral or subarachnoid haemorrhages occurred. Migraine patients were found to be at significantly increased risk for haemorrhagic stroke (OR 1.48, 95% CI 1.2–1.9; $P = 0.001$). There was no clear difference between migraine with aura (OR 1.6, 95% CI 0.9–3.0; $P = 0.13$) or migraine without aura (OR 1.4, 95% CI 0.7–2.62; $P = 0.3$), male and female patients, or younger and older subjects with migraine, although Kuo et al. (65) reported higher risks in migraine with aura, men, and patients <45 years of age. A limitation in the review by Sacco et al. (17) was that subarachnoid and intraparenchymatous haemorrhages could not be separated. Next to ischaemic stroke, patients are thus likely to be at increased risk for haemorrhagic stroke, although the mechanisms likely differ and remain to be elucidated, and subgroups most at risk still need to be identified.

Migraine as a risk factor for subclinical stroke

Posterior circulation infarcts

The population-based cross-sectional Cerebral Abnormalities in Migraine, and Epidemiological Risk Analysis (CAMERA) MRI study (n = 435) assessed whether people with migraine were are at increased risk for several types of 'silent' (or subclinical) brain lesions and whether certain areas of the brain were particularly vulnerable (66). None of the participants reported a history of stroke or transient ischaemic attack, or showed relevant abnormalities at standard neurological examination.

In the migraine with aura group, 8% of patients had one or more posterior circulation infarcts. This was significantly higher compared with controls (0.7%; $P = 0.005$) and migraineurs without aura (2%).The highest risk was found in those with migraine with aura with ≥1 attack per month (OR 15.8, 95% CI 1.8–140). Infarct size ranged from 2 to 21 mm. Most lesions were located in the cerebellum, typically in a border zone location (**Figure 3.8**). The average number of lesions per patient was 1.8. Although migraine-related clinical strokes seem to have a predilection for the occipital lobes, in the CAMERA study none of the posterior circulation infarcts was in the occipital lobes.

Migraine patients with posterior circulation infarcts were significantly older, but cardiovascular risk factors were not more prevalent, and the presence of these lesions was not significantly associated with supratentorial brain changes, such as WMLs. These two observations suggest that the lesions are not atherosclerotic in origin. The combination of vascular distribution, deep border zone location, shape, size, and imaging characteristics on MRI makes it likely that the lesions have an ischaemic origin. The most likely aetiological mechanism seems to be hypoperfusion and/or embolism rather than atherosclerosis or small vessel disease.

The higher risk for those with a higher attack frequency may point to migraine-attack related mechanisms. During and after migraine attacks, low cerebral flow below an ischaemic threshold has been described (36,37,67–69). Theoretically, a decrease in brain perfusion pressure (e.g. during migraine) affects the clearance and destination of embolic particles; narrowing of the arterial lumen and endothelial abnormalities stimulate formation of thrombi; and occlusive thrombi further reduce blood flow and brain perfusion (70). Because the deep cerebellar territories have a pattern of progressively tapering arteries with only few anastomoses present, they are likely to be particularly vulnerable to hypoperfusion-related border

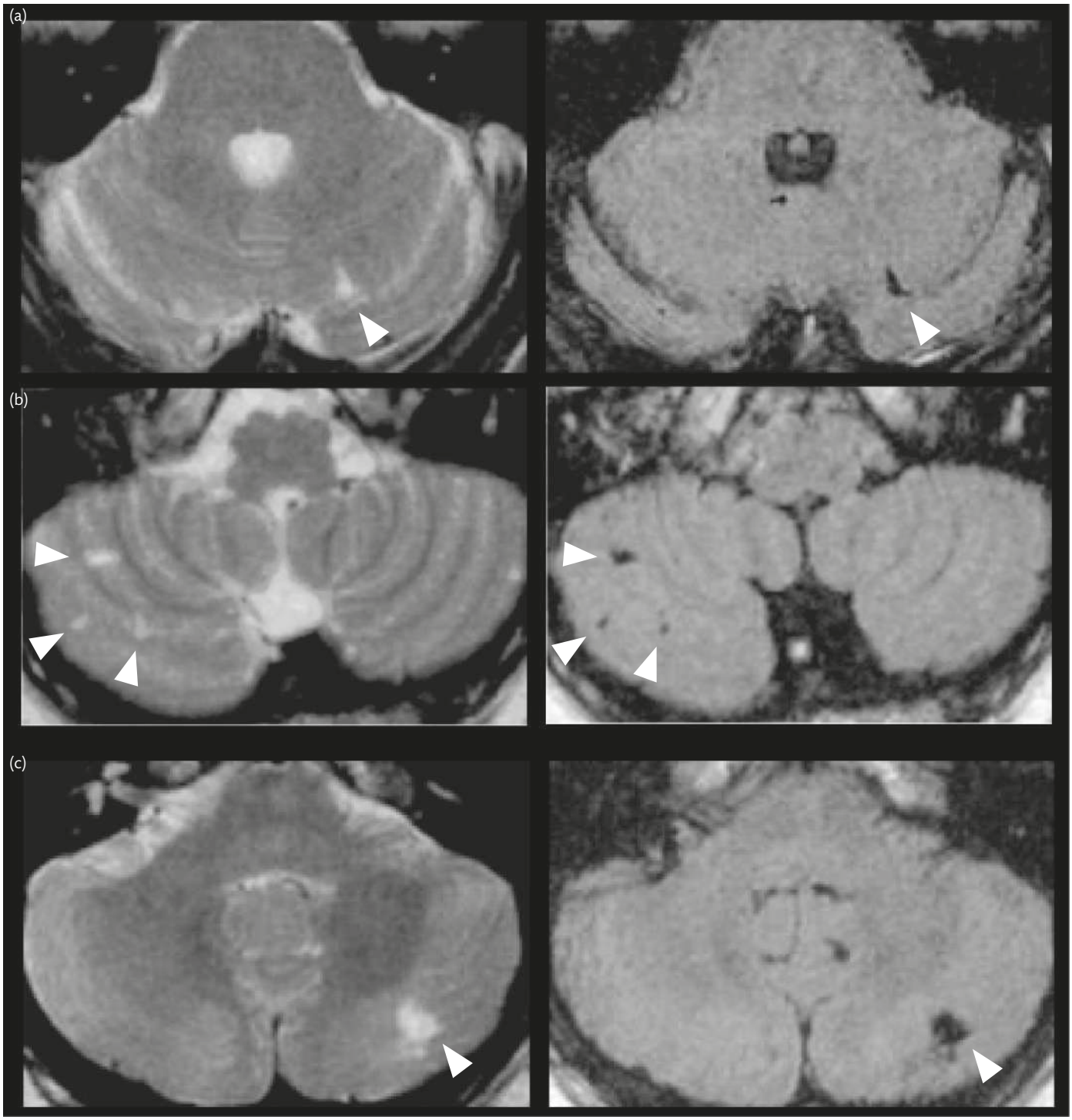

Figure 3.8 Cerebellar infarcts in patients with migraine with aura.

Corresponding T2-weighted (left) and fluid-attenuated inversion recovery (right) magnetic resonance images showing (multiple) cerebellar infarcts (arrowheads) in three migraine with aura patients from the CAMERA study.

zone infarct mechanisms (71,72). This hypoperfusion-related concept matches the findings of previous studies in which the small cerebellar border zone infarcts, in particular when multiple, were strongly associated with severe occlusive and/or (artery-to-artery) embolic disease based on vertebrobasilar atherosclerosis, likely to result in hypoperfusion and infarction.

The population-based Age, Gene/Environment Susceptibility (AGES)-Reykjavik study (n = 4689) confirmed these findings, and also reported a significantly higher prevalence of cerebellar infarcts on MRI scans in female migraine with aura patients in later life (23% vs 15%; P <0.001) (73). In that study, there was no increased risk for cortical or subcortical infarcts on MRI for migraine patients.

In the 9-year follow-up CAMERA-2 study, 66% of the original sample was rescanned with the same MRI scanners and protocols. None of the infarcts present at baseline had disappeared. Only in the migraine group had new posterior circulation infarcts occurred (5% vs 0%; P = 0.07) (20).

Other population-based evidence for silent infarcts in migraine

In the Epidemiology of Vascular Ageing study (EVA; n = 780) migraine with aura patients (n = 17) had over a threefold increased risk (OR 3.4, 95% CI 1.2–9.3) vs controls (n = 617) for any infarct on MRI, and there was a suggestion that migraine with aura patients were at increased risk for multiple infarcts (OR 3.7, 95% CI 0.8–17) (74). In this study, most infarcts were located outside the cerebellum or brainstem, and the number of patients was, unfortunately, too small for further statistical testing of specific infarct locations like cerebellum (5.9% vs 2.8%) and thalamus (11.8% vs 2.1%) in migraine with aura versus control participants.

The MRI substudy of the Northern Manhattan Study (NOMAS) included 546 racial/ethnically diverse population-based participants; 65% were Hispanic. Migraine patients had a significantly higher risk of subclinical brain infarcts (OR 2.1, 95% CI 1.0–4.2), which was even higher in migraineurs without aura (OR 2.6, 95% CI 1.3–5.5). In the groups of participants aged >75 years, 30% of migraineurs had at least one infarct on MRI versus 15% of controls. In this study, infarcts were found most commonly in the white matter (13%) and cerebellum (10%) (75).

In summary, an association between migraine and subclinical infarcts is well established by now. Similarly to clinical ischaemic stroke, migraine with aura patients are at highest risk. The exact mechanisms and potential consequences need further evaluation and research. The posterior circulation territory is probably most vulnerable in migraine patients.

Migraine and T2 hyperintensities on MRI

White matter lesions in migraine

From the early days of MRI, reports exist on the presence of WMLs on T2-weighted images in migraine patients. Initial clinic-based studies presented data on WMLs in migraine patients, but results were often uncontrolled, inconsistent, or conflicting. Some studies evaluated migraine subtypes, also with inconsistent results. One study found that migraine attack frequency was related to an increased prevalence of WMLs. Despite the various limitations and discrepancies in those MRI studies, a meta-analysis summarized the results of seven case–control studies, and reported that migraine patients were at four times increased risk (OR 3.9, 95% CI 2.3–6.7) for WMLs, regardless of comorbidities like cardiovascular risk factors, demyelinating disease, inflammatory conditions, and valvular heart disease (18).

White matter lesions in migraine: the CAMERA- 1 and CAMERA-2 studies

Because the clinic-based studies mentioned in the previous section suffered from methodological difficulties, and might have evaluated a more severe than average subgroup of migraine patients (due to their 'clinic-based' origin), the cross-sectional population-based CAMERA MRI study was carried out (see 'Migraine as a risk factor for subclinical stroke'). In women of the CAMERA cohort, the risk of having a high deep WML load (top twentieth percentile of the distribution of deep WML load; **Figure 3.9**) was increased in migraineurs versus controls (OR 2.1, 95% CI 1.0–4.1). This risk was higher in those with a higher attack frequency (≥1 attack/ per month; OR 2.6, 95% CI 1.2–5.7), and was similar among women with migraine with and without aura. Among men, the prevalence of deep WMLs did not differ between controls and migraineurs. No association was found between the severity of periventricular WMLs and migraine, irrespective of sex or migraine frequency or subtype.

The finding of higher risks in those with a higher attack frequency was suggestive of a potential causal relationship between migraine attacks or attack severity and the development of WMLs. Therefore, the 9-year follow-up CAMERA 2 study (n = 286, mean age 57±8 years) was carried out to test for accumulative effects of recurrent attacks and to study the underlying mechanisms and possible cognitive consequences (20).

In the follow-up study, again there were no differences in WMLs between male participants with migraine versus controls. However, deep WML volume was higher in female migraineurs than in controls (P = 0.04), and their deep WML progression was more severe (77% vs 60%; P = 0.02), which was highest in those with migraine without aura (83%). Multivariate logistic regression showed that migraine was independently associated with deep WML progression (OR 2.1, 95% CI 1.0–4.1; P = 0.04). The increase in total deep WML volume was explained by an increased number of new lesions, rather than by an increase in size of pre-existing lesions. **Figure 3.10** shows an example of incident lesions in a female migraine patient after 9 years of follow-up. The mean size of individual hyperintensities at follow-up did not differ between participants with migraine and controls. Among females with migraine, deep WMLs appeared to be more diffusely distributed than in controls (**Figure 3.11**). Hypertension and diabetes were not associated with a higher incidence of deep white matter hyperintensity progression. Exploratory analyses showed no association of number of migraine attacks, migraine attack duration, migraine frequency, type of attack, or migraine therapy with deep WML progression. There was also a lack of significant decline in cognitive function correlated with WMLs in the CAMERA-2 study.

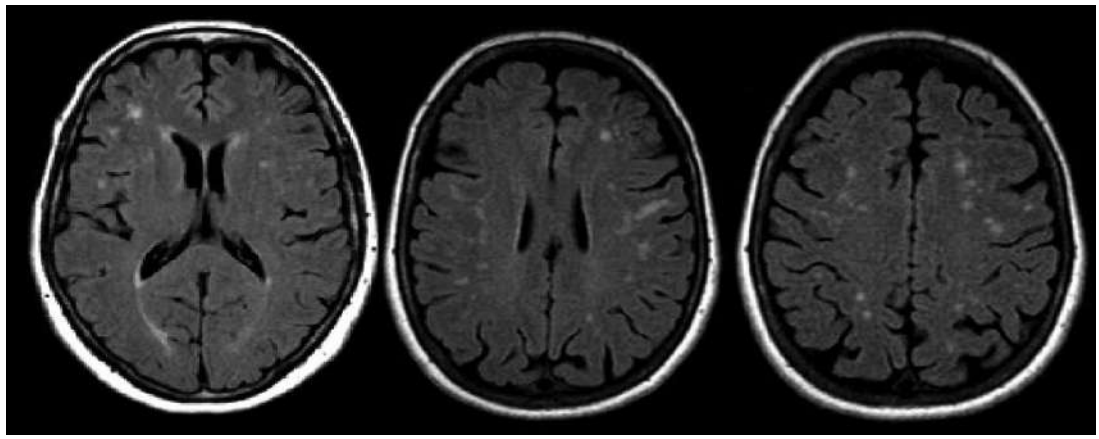

Figure 3.9 Focal small-to-medium-sized deep white matter lesions in a 47-year-old woman with migraine.

White matter lesions in migraine: other population-based evidence

In the longitudinal EVA study (n = 780; mean age 69 ± 3 years), participants with a history of any severe headache (including migraine) were at increased risk of higher WML volumes (OR 2.0, 95% CI 1.3–3.1) versus controls, with similar findings for deep and periventricular WMLs (74). In participants with migraine with aura the associations with WMLs were strongest.

A subset of participants of the Atherosclerosis Risk in Communities (ARIC) cohort study (n = 1028) received two MRI examinations, 8–12 years apart. The authors also showed, in a cross-sectional analysis, that migraine without aura is associated with WMLs (OR 1.9, 95% CI 1.0–3.4). However, they failed to demonstrate that migraine was associated with WML volume progression. Differences in lesion-quantification methodology, in the definition of progression, in the older age, size and other characteristics of the cohort, and so on, might explain why the findings seem to contrast with the findings of the CAMERA-2 study.

Unexpectedly, in the NOMAS study (n = 546; two-thirds of participants were >60 years of age), no association between WML volume and migraine or its subgroups was found. The authors suggested that no difference was detected because of the high burden of other cardiovascular risk factors in the racially diverse older cohort.

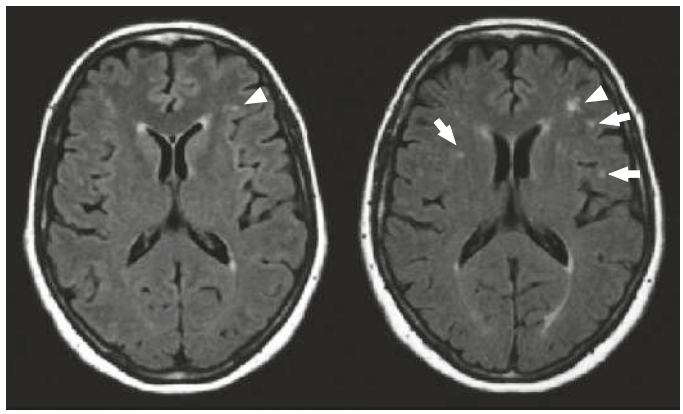

Figure 3.10 Fluid-attenuated inversion recovery images showing pre-existing (arrowhead) and newly developed (arrows) deep white matter lesions after 9 years of follow-up in a 37-year-old (at baseline) female migraine without aura patient.

Pathophysiological mechanisms?

Although the pathological substrate of WMLs in migraine remains unknown, the most likely histological substrate of these abnormalities is incomplete infarction with changes such as gliosis and demyelination (76). The causative mechanisms, however, remain largely unknown. Different explanatory options have been described.

Attack-related mechanisms may play a role, as was suggested by the higher risk of WMLs in the CAMERA-1 study, and as seems likely given the occurrences of migrainous infarcts. During attacks, reduced blood flow in large and/or small arteries (37,69), possibly in combination with vasoconstriction or activation of the clotting system/platelets (77,78), might lead to formation of local thrombi. Alternatively, local tissue changes during migraine attacks, such as excessive neuronal activation, neurogenic inflammation, neuropeptide and cytokine release (79), or excitotoxity (80), may occur and such changes may lead directly to tissue damage. Reversible MRI abnormalities during migraine aura, including areas of increased vasogenic leakage (46) and evidence of blood–brain barrier dysfunction in prolonged aura (40,41,44) seem to illustrate the possibility of direct effects to the brain during attacks, most likely first acting on the level of the microvasculature (81), and possibly being enhanced by other factors like a matrix metalloproteinase-9 dependent cascade mechanism, which may increase the risk of local tissue damage (82).

However, because the progression of WMLs and occurrence of infarcts in the CAMERA cohort was not dependent on persisting migraine activity, and also because of the attack-unrelated increased risk of clinical ischaemic strokes in migraineurs, *attack-unrelated factors* also seem to play a role. With increasing age, when attacks generally diminish, other systemic migraine 'disease-related' conditions leading to WMLs are possibly increasing, and likely complicate the detection of attack-related mechanisms. Attack-unrelated factors could, for example, include chronic procoagulatory or pro-inflammatory changes due to endothelial dysfunction (83,84), elevated homocysteine levels (85–87), or recurrent paradoxical (micro-)

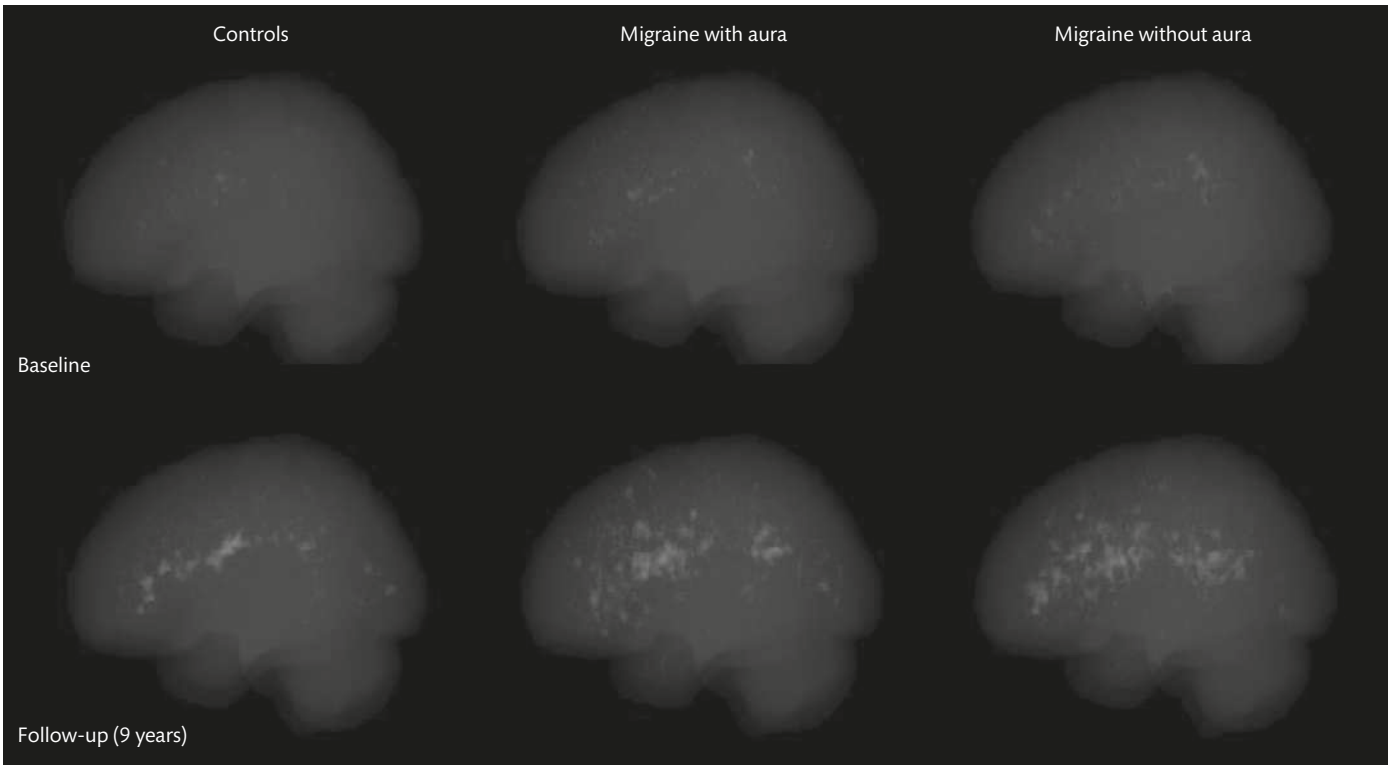

Figure 3.11 (see Colour Plate section) Topography and progression of deep white matter lesions (WMLs) in female migraine patients and controls

Baseline and follow-up deep WMLs are projected on transparent three-dimensional maps (normalized for differences in group size; controls, n = 52; migraine with aura, n = 75; migraine without aura, n = 57).

emboli due to right-to-left shunts (88). In addition, population-based evidence that migraine (with aura) is associated with a higher cardiovascular risk profile might contribute to the risk of (ischaemic) brain lesions (89).

Brainstem lesions

In the CAMERA-1 study, infratentorial hyperintense lesions (IHLs) were also significantly more prevalent in migraine patients (4.4.%) compared with controls (0.7%; $P = 0.04$) (67). The majority of the IHLs were located in the pons. The CAMERA-2 study showed that after 9 years of follow-up the prevalence of IHLs remained higher in women with versus without migraine (21% vs 4%; adjusted OR 6.5, 95% CI 1.5–28.3 ($P = 0.01$)), and that they also more often showed progression of IHLs (15% vs 2%; adjusted OR 7.7, 95% CI 1.0–59.5 ($P = 0.05$)) (20). **Figure 3.12** shows typical examples of T2 hyperintensities in the brainstem and their progression over time.

Typically, brainstem lesions were located in the dorsal basis pontis, adjacent to the tegmentum, at the level of, and slightly cranial to, the entry zone of the trigeminal nerve. In nearly all cases lesions were located bilaterally, sometimes extending to the midline; none reached the surface of the pons. Hyperintensities seem to involve the pontocerebellar fibres, the pontine nuclei, or the nucleus reticularis tegmenti pontis, and, in some cases, parts of the corticopontine (pyramidal tract) or medial lemniscus fibres. These anatomical locations are supplied by the anteromedial and anterolateral groups arising from the basilar artery.

Earlier reports in non-migraineurs linked pontine IHLs to patients with cardiovascular risk factors, leukoaraiosis, lacunar infarcts, and poor clinical outcome after stroke (90–92). Histopathologically, pontine IHLs correspond to myelin pallor and reactive astrocytosis. The pathophysiology of these lesions is assumed to be comparable as for lesions in subcortical arteriosclerotic encephalopathy (i.e. ischaemia secondary to small artery sclerosis). There is a good correlation between MRI findings and histopathology (90). Similar hyperintense brainstem lesions are also frequent in cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), a disorder in which migraine with aura is often the presenting symptom (93). In CADASIL, decreased cerebral perfusion secondary to changes in the wall of cerebral arteries leads to early damage of the white matter. Regions that are irrigated by the longest perforating arteries are most vulnerable to hypoperfusion. This is particularly the case for the central part of the pons. Similarly, as discussed earlier for deep WMLs, migraine attacks might causally be related to the brainstem lesions, because repeated or prolonged reduced perfusion has been described in migraine attacks, although not specifically in the pons (69). Alternatively, attack-unrelated 'systemic' factors could also explain the association, maybe in combination with suggested impaired adaptive cerebral haemodynamic mechanisms in the posterior circulation of migraine patients (94).

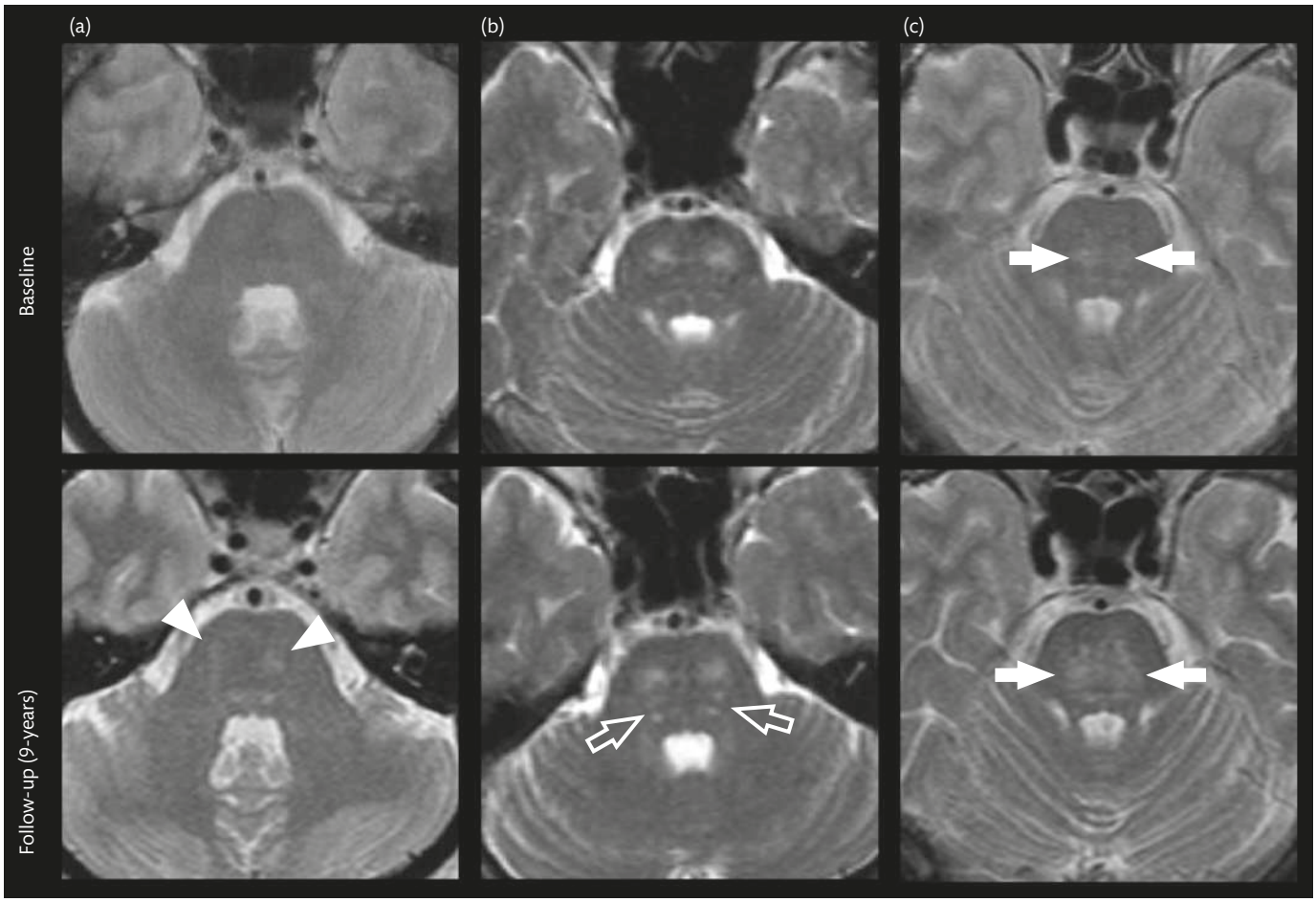

Figure 3.12 Infratentorial hyperintense lesions (IHLs) in migraine.

T2-weighted images of baseline and 9-year follow-up of three migraine patients from the CAMERA study, showing increasing loads of IHLs: either (a) newly developed lesions (arrowheads), (b) additional lesions (open arrows), or (c) increases in size (arrows), compared to baseline.

'Subclinical' MRI findings in the individual migraine patient

The knowledge from hospital- and population-based studies that migraine is an independent risk factor for deep WMLs, IHLs, and subclinical infarcts does not imply that when such lesions are identified on a brain MRI scan in a migraine patient that migraine is 'the cause'. In routine neuroradiological practice, T2 hyperintense lesions in the white matter are frequently encountered in those older than 50 years of age, but also appear in younger individuals. No studies found clear preferential locations or distribution patterns for patients with migraine with WMLs. Therefore, in most patients with migraine and WMLs, the lesions will remain 'non-specific'. The identification of a limited number of small-to-medium-sized lesions in adults with migraine does therefore generally not need further medical attention.

Incidentally, WMLs are observed on MRI scans in relatively young patients (e.g. <40 years of age). In such cases, the number, location, aspect, and distribution of the lesions have to be carefully evaluated, and based on the images and clinical history together, the likelihood of other diseases that are associated with WMLs (such as multiple sclerosis; vasculitis; CADASIL; mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; coagulation disorders; cardiac abnormalities, etc.) has to be considered. 'Migraine' is part of this differential diagnostic list, but other options should never be disregarded.

Similarly, the identification of one or more silent cerebellar infarcts on an MRI scan cannot directly be attributed to 'migraine', although this finding—with the data from the CAMERA stud, showing that 8% of patients with migraine with aura from the general population affected—is not so unusual in migraine patients with aura. In such cases, if the observation is incidental, no direct clinical consequence seems to be necessary. If future research indicates that there is a risk of progression of number or size of lesions, or if there are associated functional consequences, an additional study of causes and evaluation of the usefulness of preventive therapy has to be initiated. However, a patient who presents with an acute cerebellar infarct, irrespective of the size of the lesion or presence of migraine, has to be screened for (embolic) sources of the infarction, and treated accordingly.

Conclusion

Migraine is a prevalent disorder. Knowledge of the pathophysiology of migraine allows better interpretation of neuroimaging findings in migraine patients, who may present both in acute situations and in regular outpatient settings.

A migraine patient may present during a migraine attack with neurological deficits. Normal neurological aura symptoms need to be differentiated from 'prolonged aura' and ischaemic stroke. When a clinical diagnosis is not possible, urgent neuroimaging is mandatory. Neuroimaging may show heterogeneous changes during 'prolonged aura', which can mostly be differentiated from findings in true ischaemia. If ischaemia is identified during a migraine attack, this might be either due to true migrainous infarction, to ischaemic stroke co-existing with migraine, or to cerebral infarction of other cause presenting with symptoms resembling migraine with aura.

Migraine patients, notably those with aura, and in the younger age category, are also at increased risk of clinical ischaemic or haemorrhagic stroke unrelated to a migraine attack. The exact mechanisms behind these associations are still unknown, although attack-unrelated 'systemic' pro-inflammatory, prothrombotic, endothelial, cardiac, and genetic factors probably play a role, and may be part of 'migraine as a disease'. Migraine is associated with subclinical infarcts, and supratentorial and infratentorial T2 hyperintense lesions on MRI. The higher prevalence of such lesions is probably explained by similar pathophysiological mechanisms.

Neuroimaging in migraine patients is overused in non-acute situations; recommendations have been formulated to identify patients in whom neuroimaging is warranted.

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4

Headache mechanisms

Andrew Charles

Changing paradigms regarding headache mechanisms: moving away from vascular hypothesis

Migraine and cluster headache were, for decades, considered to be 'vascular headaches', based on the presumption that the vasculature played a primary role in headache pain in these disorders. However, extensive recent studies have shown that changes in the calibre of either extracranial or intracranial vessels are neither necessary nor sufficient to cause migraine pain. Recent high-resolution magnetic resonance angiography studies have shown that the neither evoked nor spontaneous migraine headache are correlated with the dilation of intracranial or extracranial arteries (1,2). Furthermore, significant vasodilation evoked by substances such as vasoactive intestinal peptide is not necessarily correlated with headache (3). Thus, while significant vascular changes may occur with some types of primary headache, it is likely that these changes are a reflection of activity in the brain and in perivascular nerves that are responsible for headache, rather than representing a primary cause of pain. It is now clear that acute and preventive headache therapies do not work primarily by constricting blood vessels or by preventing vasodilation (2).

Consistent with the vascular hypothesis of headache, the throbbing quality of migraine and other types of headache was presumed to be a reflection of aberrant sensitivity to vascular pulsation. Recent studies, however, provide strong evidence against this presumption. When examined quantitatively, the 'throb rate' of migraine pain is generally significantly slower than that of the arterial pulse, and their phase is not consistently correlated (4). This observation indicates that other mechanisms must be involved in the throbbing nature of migraine headache; one possibility is that this could be a reflection of slow oscillations in cellular activity in the thalamus or brainstem.

Migraine mechanisms

The predisposition to migraine

The genetics of migraine provide important information about migraine pathophysiology. Migraine has a substantial genetic component, but apart from the rare hemiplegic migraine syndromes, most familial migraine is unlikely to involve a single gene. Rather, combinations of multiple genes and epigenetic factors are involved. Of the genes that predispose to migraine that have been identified thus far, there is no single unifying mechanism that is common to all of them. It is interesting to consider how such a diverse array of genes can ultimately contribute to the same clinical phenomenon. A better understanding of the final common pathways through which these genes predispose to migraine is likely to lead to more definitive acute and preventive therapies (see **Figure 4.1**).

Neurophysiological changes in migraine patients

A variety of clinical neurophysiology approaches indicate alterations in brain excitability, connectivity, and sensory processing between attacks in migraine patients. Among these alterations are increased photic driving and synchronization of specific electroencephalography (EEG) rhythms between attacks (5–8). Between attacks, migraine patients have also been found to have reduced habituation of cortical responses and reflexes evoked by either repetitive noxious or non-noxious stimuli (9–13). The habituation of cortical responses to non-noxious stimuli normalizes during attacks. Further, the amplitude of high-frequency oscillations in somatosensory-evoked responses, a pattern of activity believed to reflect connectivity between the thalamus and cortex, is higher in migraine patients between attacks than in controls, and also normalizes during attacks (14,15). Whether these differences between migraine patients interictally and controls reflect increased or decreased brain excitability remains the subject of debate, but it seems clear that the excitability of the 'migraine brain' is more variable that that of those without migraine. Taken together, the differences suggest that migraine involves dysregulation of normal coordination between the activity of the thalamus and the cortex (16).

The serotonin hypothesis

A number of studies, primarily measuring serum and platelet levels of serotonin, have suggested that interictal serotonin levels are lower in patients with migraine than in controls (17,18). Functional imaging studies also suggest alterations in serotonin and/or its receptors in migraine patients between attacks. A single photon emission computed tomography study using a radioactive ligand targeting the brain serotonin transporter found significantly increased binding of the ligand in the brainstem as compared with controls, consistent with either low levels of serotonin or higher levels of the transporter

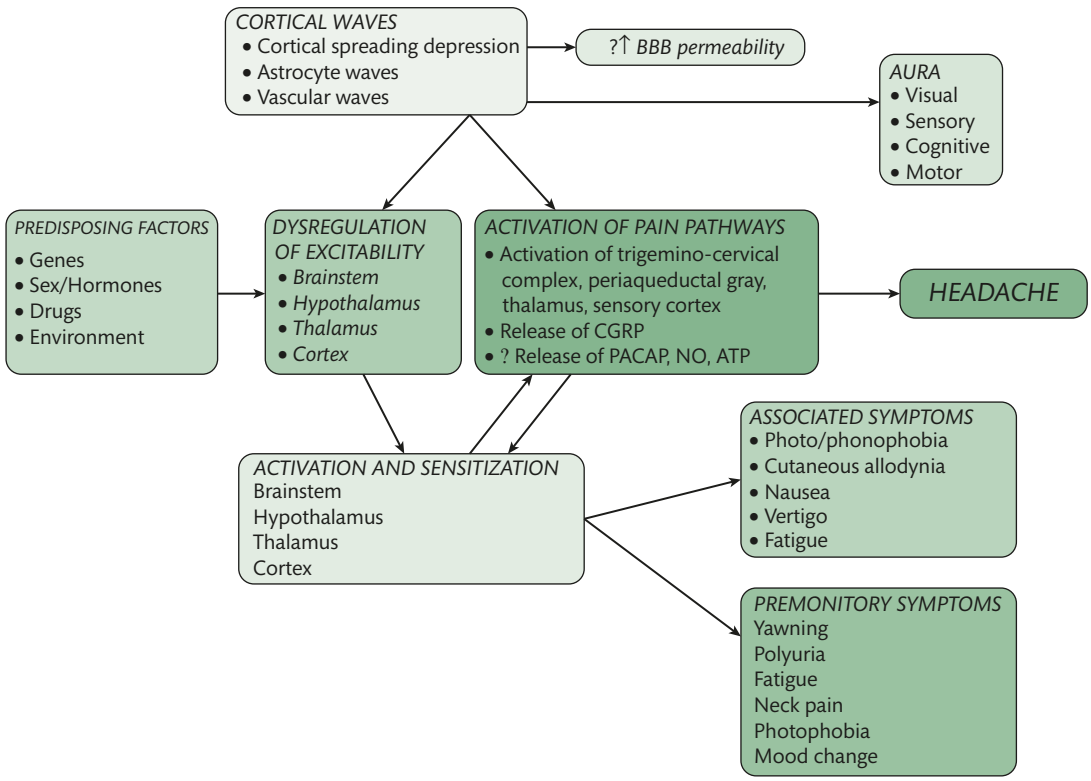

Figure 4.1 Schematic of basic mechanisms of migraine.
BBB, blood–brain barrier; CGRP, calcitonin gene-related peptide; NO, nitric oxide; ATP, adenosine triphosphate.

(19). Similarly, a positron emission tomography (PET) study showed increased brain binding of a ligand specific for the 1A subtype of serotonin receptors (5-hydroxytryptamine (5-HT)$_{1A}$ receptors) between attacks in patients with migraine without aura, consistent either with reduced levels of serotonin or an increased density 5-HT$_{1A}$ receptors in migraine patients (20). A PET study using a radioactive marker of 5-HT synthesis found that global brain 5-HT synthetic rate was slightly but not significantly reduced in migraine patients between attacks compared with controls (21). Administration of the 5-HT$_1$ agonist buspirone was reported to evoke a significantly greater release of prolactin in migraine patients in the interictal state compared with controls, suggesting increased central 5-HT$_1$ receptor sensitivity in migraine patients between attacks (22). These studies all point toward low levels of serotonin in migraine patients between attacks, suggesting that these reduced central nervous system serotonin levels could increase the propensity to migraine. As with many of the neurochemical and physiological changes observed in migraine, it is not clear whether these observed changes in serotonin are a cause or effect of migraine. While the efficacy of triptans, selective agonists of 5-HT$_{1B}$, D, and F receptors, suggests a role for serotonin in migraine therapy, the lack of efficacy of most selective serotonin uptake inhibitors as migraine preventive therapies argues against low levels of brain serotonin as a primary causative mechanism of migraine. Regardless of the exact role of the serotonin system in migraine, it clearly remains a critically important therapeutic target.

The premonitory phase

A significant percentage of migraine patients consistently experience multiple symptoms prior to the onset of aura or headache (see also Chapter 6), including light sensitivity, neck pain, fatigue, yawning, mood change, and polyuria, among others (23–25). These symptoms may occur up to several hours before headache, and some individuals can reliably identify the onset of a migraine attack based on these symptoms (26). PET studies in the premonitory phase in triggered migraine have now identified changes in brain activity that are correlated with these symptoms, including the posterolateral hypothalamus, midbrain tegmental area, periaqueductal gray, dorsal pons, and cortical areas, including occipital, temporal, and prefrontal cortex (27). As discussed earlier, electrophysiological studies also indicate significant changes in brain function in the hours prior to headache.

Although both imaging and clinical neurophysiological studies indicate that widespread changes in brain excitability occur before headache, one particular brain region that may play a critical role is the hypothalamus. Changes in mood, appetite, and energy that precede headache are suggestive of alteration in hypothalamic function, and functional imaging studies demonstrating increased blood flow in the hypothalamus both before and during migraine attacks support an important role for this brain region (27,28). This is of particular interest because multiple hypothalamic peptides may therefore represent novel targets for therapies that could be administered during the premonitory phase of headache, rather than during later phases of an attack during which all therapies may be less effective. One example of a such a hypothalamic target is the orexins, which show promise in animal models as potential mediators of migraine and therapeutic targets (29).

The fact that some of premonitory symptoms can also be evoked by dopamine agonists led to the hypothesis that the premonitory phase

of migraine involves the release of dopamine (30,31). The observation in a small study that the dopamine antagonist domperidone could abort an impending attack even when taken before headache supported this hypothesis (32), although this finding has not been validated in further studies.

Migraine and other primary headache disorders commonly have sensitivity to light, sound, touch, and smell as prominent symptoms. This increased sensory sensitivity is generally considered to reflect 'central sensitization', i.e. changes in sensory processing in the brain or spinal cord that amplify peripheral sensory signals. In traditional pain models, central sensitization occurs as a secondary consequence of the transmission of pain signals from the periphery. In migraine and other headache disorders, however, sensory sensitivity may precede pain by up to hours (26,33), and this prodromal sensory sensitivity may be correlated with changes in the activity of related brain regions (27). The early occurrence of sensory sensitivity before pain indicates that, contrary to traditional pain models, central sensitization in headache can be a primary event rather than a secondary consequence of painful input from the peripheral nervous system.

Migraine aura

Migraine aura is defined as a transient change in vision, somatic sensation, language, motor function, or brainstem function that precedes or accompanies headache. Approximately 30–40% of migraine patients experience at least two auras in their life, and therefore qualify for a diagnosis of migraine with aura (34,35). The visual, sensory, language, and motor symptoms are caused by alterations in cortical function that may propagate from one region to another. While traditionally considered to be a distinct phase of a migraine attack that triggers subsequent symptoms, including pain, prospective examination of the timing of migraine symptoms relative to aura indicates that headache and other migraine symptoms commonly occur simultaneously with aura (36). These observations suggest that the pain and associated symptoms of migraine may occur in parallel with aura, rather than as a direct downstream consequence of the aura phenomenon.

Clinical features of the visual aura

The classic migraine visual aura is a 'scintillating scotoma', a flickering, bright, typically jagged front that expands in multiple directions over a few minutes to 30 minutes, leaving its wake an area of decreased or absent vision (37) (see also Chapter 6). It is important to recognize, however, that this visual phenomenon is, in fact, only one of a variety of visual phenomena that can be part of the migraine visual aura. Flashing lights, scotomas without a positive edge, colours in the visual field, or simply distortion of vision are also commonly reported (38,39). It is also common for these visual phenomena to be stationary and fixed in size, rather than the classically expanding visual percept.

Systematic detailed recording of migraine aura percepts by individuals have revealed a number of important features (40). Firstly, they may begin in different regions of the visual field, indicating that the underlying phenomenon is not invariably initiated at a single cortical focus. Secondly, the pattern of spread in the visual field is not necessarily consistent with a concentric spread in the visual cortex, but rather may be more consistent with a wave of fixed width travelling along a single sulcus or gyrus. Thirdly, even with an attentive observer, the visual phenomenon may disappear for minutes at time, before reappearing in a location consistent with the concept that the wave has propagated through a region of cortex without producing any symptoms. This observation raises the possibility that 'silent aura' may, indeed, occur when the underlying change in cortical activity occurs in a region of cortex that does not generate any positive or negative neurological symptoms.

Imaging studies of the migraine aura

Functional imaging studies have shown significant changes in brain metabolism and blood flow in some patients during migraine aura (41–43). The most commonly seen change is hypoperfusion (44), although hyperperfusion may also occur (45). PET studies have also shown decreased metabolism in association with migraine aura (46). It is not clear whether or not these changes occur universally in patients with migraine aura, as clinical experience and case reports (47) indicate that many patients have normal computed tomography and magnetic resonance imaging (MRI) scans while experiencing aura. In cases of prolonged aura or hemiplegic migraine, vasogenic oedema and breakdown of the blood–brain barrier may be observed (48–50). There may be disruption of the normal coupling between brain activity and blood flow during migraine aura. Hypometabolism in the presence of normal blood flow has been reported (46,48,51), and studies using transcranial Doppler have shown impaired vascular reactivity during a migraine aura or headache (52).

Cortical spreading depression

Cortical spreading depression (CSD) is a wave of excitation followed by inhibition of neural and glial activity that propagates slow across the brain surface. The temporal characteristics of CSD are very similar to those of the spread of the visual percept of the migraine aura across the visual cortex. This similarity led to the assumption, which has been held since the original description of CSD in the 1940s, that CSD is the physiological substrate of the migraine aura (53). CSD in humans with brain injury has now been extensively characterized using electrodes placed directly on the brain surface (54,55). While changes suggestive of CSD have been observed with magnetoencephalography in migraine patients (56), the definitive electrophysiological features of CSD have never been observed in migraine. This may be because standard surface EEG recordings do not detect the phenomenon. Regardless, it is important to recognize that we are still without definitive proof that CSD, as it is observed in animal models or in brain injury, is the same physiological phenomenon that underlies migraine aura.

Evidence from experimental models provides strong circumstantial support for a role of CSD in migraine. Three different gene mutations associated with familial hemiplegic migraine, as well as one mutation associated with familial migraine with and without aura, each reduces the threshold for induction of CSD (57–60). The threshold for induction of CSD is also reduced by female sex, as well as by oestrogen, consistent with the significantly higher prevalence of migraine in women compared with men (58,61). Finally, multiple established migraine preventive medications with diverse mechanisms of action have all been reported to inhibit CSD, whereas related medications that do not prevent migraine do not inhibit CSD (62–64). While there are some exceptions to CSD as a predictive model (65), the majority of known migraine preventive therapies tested to date have been reported to inhibit CSD.

In rodents or other animal models which have a lissencephalic cortex (no sulci or gyri), CSD expands as a concentric wave, like that produced by a pebble in a pond. As discussed, however, analysis of the percept of the visual aura suggests that the alteration in cortical activity underlying migraine aura may travel with more limited expansion along individual sulci or gyri. Several experimental triggers can evoke CSD in animal models, including local mechanical stimulation or injury, tetanic or DC electrical stimulation, KCl, $CaCl_2$, hypo-osmotic medium, metabolic inhibitors, ouabain, glutamate receptor agonists, endothelin, and microemboli (66). Elevations in extracellular K^+ and activation of glutamate receptors appear to play key roles in the initiation of CSD (67–73). As discussed, it is well demonstrated that brain injury can trigger CSD in humans. For migraine, however, the mechanisms underlying the spontaneous occurrence of CSD are not clear. It is possible that multiple different cellular pathways, perhaps driven by different genetic variations, could lead to spontaneous increases in K^+ and glutamate release through distinct mechanisms in different individuals.

Neurovascular uncoupling with CSD

Both in rodent models and in humans, the propagated wave of CSD can be followed by sustained uncoupling of the normal vascular response to neural activity. In rodents, vasoconstriction and decreased blood flow persist for up to an hour in the face of a prolonged membrane depolarization and recovery of neuronal activity (74,75). Delayed activation of trigeminal nociceptors following CSD has been reported, raising the possibility that the prolonged neurovascular uncoupling that follows CSD contributes to the activation of pain by this phenomenon (76).

CSD as a cause of headache?

CSD in animal models is associated with release of a number of messengers that could be involved in the generation of headache, including nitric oxide (77,78), adenosine triphosphate (79), calcitonin gene-related peptide (CGRP) (80–83), and high-mobility group box 1 (84). CSD has been shown to cause activation of trigeminal nociceptive neurons as indicated by immunohistological labelling for c-Fos in the brainstem (85), as well as by electrophysiological recording of neurons in the trigeminal ganglion and brainstem (76,86). CSD has also been reported to cause changes in the activity of brainstem neurons responsible for trigeminal pain processing directly via descending central pathways (87,88), indicating that CSD may influence subcortical regions implicated in migraine headache directly, without the requirement for trigeminal or other peripheral input.

Whether or not CSD as it occurs in animal models is, indeed, the mechanism underlying the migraine aura remains an open question. Similarly, the potential role of CSD as a trigger for the headache of migraine remains unresolved. It is possible that CSD is a manifestation of neurochemical and cellular changes that are occurring diffusely in the brain during a migraine attack, rather than it being a fundamental cause of headache. Advances in imaging and non-invasive electrophysiological techniques are likely to provide more definitive information about the occurrence of CSD in migraine and its role in causing the symptoms of a migraine attack.

The headache phase

The anatomy of headache

The trigeminal nerve

The trigeminal nerve is believed to be primarily responsible for carrying pain signals that are responsible for headache for migraine and other primary headache disorders. The ophthalmic division (V1) of the trigeminal nerve innervates the dura of the anterior cranial fossa (89). Branches of V1 travel with branches of the middle meningeal artery, and also along the superior sagittal sinus. A recurrent meningeal branch of V1, the nervus tentorii of Arnold, innervates the dura mater of the parieto-occipital region, the tentorium cerebelli, the posterior third of the falx cerebri, and the superior sagittal and transverse sinuses (89). Branches of the V2 and V3 divisions of the trigeminal nerve are also believed to innervate the middle cranial fossa. Recent studies in humans and rodents have shown that trigeminal meningeal afferents may have extracranial projections (90,91), raising the possibility that this could be a pathway by which extracranial triggers (and therapies) could modulate intracranial mechanisms of migraine.

The cervical nerves and the trigeminocervical complex

Although multiple primary headache disorders are commonly referred to as 'trigeminovascular' disorders, it is important to recognize that other nerves apart from the trigeminal nerve may also play important roles. The first three cervical nerves (C1, C2, and C3), in particular, may be important mediators of primary headaches. Patients commonly report neck pain in the premonitory phase or the postdromal phase of migraine, as well as during the headache phase. Animal studies and some human studies indicate that C1–C3 innervate the dura of the posterior cranial fossa (89,92,93). Pain input from the C1–C3 nerves converges with input from the trigeminal nerve in the caudal portion of the trigeminal nucleus caudalis in the medulla and cervical spinal cord, known as the trigemino-cervical complex. Animal studies indicate that stimulation of the occipital nerve (comprised of branches of C2 and C3) leads to increased firing of second-order neurons receiving trigeminal input from the sagittal sinus, and the reverse is also true (94,95). Interestingly, stimulation of rostral structures in the cervical spine in humans may evoke pain that radiates to the frontal or periorbital region (96). Selective stimulation of the C1 nerve, but not the C2 and C3 nerves, has also been shown to evoke pain around the eye in individuals with migraine (97). One explanation for these referral patterns may be the sensitization of central neurons in the trigemino-cervical complex, with overlapping central representations of input from trigeminal and cervical inputs.

Other brain regions implicated in migraine pain include the periaqueductal gray, the dorsolateral pons, the rostral ventromedial medulla, the thalamus, and the parietal cortex (98). Stimulation of the periaqueductal gray in the brainstem has been reported to evoke migraine-like headache (99), and in animal models this region contains 5-HT_{1B} and 5-HT_{1D} receptors that are activated by triptans (100). PET studies have consistently shown activation of the dorsolateral pons during migraine attacks, particularly on the side ipsilateral to the pain (101). Increased activation of the thalamus has been visualized with functional MRI (fMRI) in migraine patients who have widespread allodynia associated with their attacks (102).

Whether activation of these regions is a cause or a consequence of migraine headache, or activation of any region is specific to migraine as compared with other types of pain, remain open questions.

The pharmacology of headache

The triptans, selective agonists at 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors, are remarkably effective in aborting a migraine attack, indicating a key role for serotonin in the inhibition of migraine. Despite their clear role as a potent modulator of migraine, however, the location and mechanism of action of the triptans remains uncertain. A key unanswered question is whether the primary site of the therapeutic action of triptans is outside of the brain, within the brain, or both. Triptans were developed as migraine therapeutics based primarily on their actions as constrictors of meningeal vessels (103). Animal studies, however, have shown that 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors are all expressed in the brain and have antinociceptive functions at multiple central sites (104). In animals models, triptans have been shown to inhibit nociceptive signalling in the trigeminal nucleus caudalis, periaqueductal gray, and thalamus (100,105,106). Whether or not triptans in fact reach these central sites of action, and whether one or more of them is a critical site responsible for therapeutic efficacy, remains unknown. The reported efficacy of lasmiditan, a non-triptan selective 5-HT_{1F} receptor agonist, indicates a non-vascular mechanism of action given that 5-HT_{1F} receptors are not widely expressed in the vasculature, and activation of these receptors does not cause any change in vascular calibre (107–109). Further, the dose-dependent dizziness, vertigo, and fatigue associated with this therapy indicate a central mechanism of action (108). Nonetheless, whether the triptans act centrally or peripherally continues to be the subject of ongoing debate.

PET studies have also provided evidence regarding serotonin receptor involvement in a migraine attack. Studies using the 5-HT_{1A} receptor-specific ligand [18F]-2'-methoxyphenyl-(N-2'-pyridinyl) -p-fluoro-benzamidoethyipiperazine ([18F]-MPPF) indicate increased 5-HT_{1A} receptor availability in the several brain regions in triggered migraine attacks (110). These studies suggest a generalized reduction in serotonergic activity during a migraine attack, and raise the possibility that in addition to other 5-HT_1 receptor subtypes, the 5-HT_{1A} receptor may play a significant role in migraine.

Calcitonin gene-related peptide

CGRP is a neuropeptide that is found throughout the body and is believed to play a variety of physiological roles, particularly in the recovery of normal vascular calibrw after vasoconstriction (111). Substantial human evidence indicates that CGRP plays a primary role in migraine. Levels of CGRP in serum have been reported to be elevated during both spontaneous and nitroglycerin-evoked migraine and cluster headache attacks versus baseline (112–115). Salivary CGRP levels have also been reported to be elevated during migraine attacks in patients with episodic migraine (116), and both serum and salivary CGRP levels may be reduced in association with pain relief achieved by treatment with a triptan (113,114,116,117). Administration of intravenous CGRP causes a delayed migraine attack in susceptible individuals, and this migraine can be effectively treated with sumatriptan (118–120). Finally, CGRP receptor antagonists and antibodies targeting CGRP have been shown to be effective as acute and preventive migraine therapies. An initial study with the CGRP receptor antagonist olcegepant delivered intravenously (121), and subsequent studies of the oral CGRP antagonist telcagepant (122,123), all showed efficacy of these agents as acute migraine therapies. More recently, antibodies to the CGRP peptide delivered either intravenously or subcutaneously have shown efficacy as preventive therapies for migraine (124–127).

The location of CGRP's effects in migraine remain unclear. As with 5-HT_{1B}, 5-HT_{1D}, and 5-HT_{1F} receptors, CGRP and its receptors are found in multiple locations in peripheral and central nociceptive and pain-modulating pathways that could play a role in migraine. CGRP and/or its receptors have been identified in sensory fibres in the dura, in neurons and satellite glia in the trigeminal ganglion, in the trigeminal nucleus caudalis, in multiple nuclei in the thalamus, and in the somatosensory cortex, insula, amygdala, hypothalamus, and nucleus raphe magnus (128–130). These locations indicate functions of CGRP in peripheral and central pain transmission, and potentially in descending modulation of pain, the response to stress and anxiety, and visual and auditory perception.

A PET study with a CGRP ligand indicating brain CGRP receptor occupancy found that the ligand was not displaced by therapeutic concentrations of telcagepant, suggesting that telcagepant could be effective without acting centrally (131). Similarly, the preventive efficacy of anti-CGRP antibodies, which presumably do not cross the blood–brain barrier, indicate that 'neutralizing' CGRP peripherally can effectively prevent migraine. While these results suggest that peripheral sites of CGRP are most important with migraine, it may be that, as with triptans, CGRP receptor or peptide antagonists may exert their therapeutic effects through duplicative actions at multiple peripheral and central sites.

Pituitary adenylate cyclase-activating peptide

Pituitary adenylate cyclase-activating peptide (PACAP) is a peptide similar to CGRP that has also been implicated in migraine. Like CGRP, administration of PACAP to susceptible individuals triggers a delayed migraine attack (132,133). Serum PACAP levels were also reported to be elevated during a migraine attack, as compared with between attacks in patients with episodic migraine (134), and administration of PACAP38 results in an increase in plasma levels of PACAP38 prior to the onset of migraine (133). As with CGRP, PACAP and its receptors are expressed in multiple regions believed to involved in migraine, including the trigeminal ganglion, sphenopalatine ganglion, trigeminal nucleus caudalis, hypothalamus, and thalamus (135–137).

PACAP binds to three different receptors, two of which are also activated by vasoactive intestinal peptide (VIP) (138). Interestingly, administration of VIP causes significant cerebral vasodilation but does consistently cause migraine, even in susceptible individuals (3). This has led to the conclusion that the PAC1 receptor, which is bound with significantly higher affinity by PACAP compared with VIP, is the receptor primarily involved in PACAP's role in migraine (133).

Prostaglandins

Triggered migraine studies also indicate that prostaglandins may play a key role in migraine.

Infusion of either prostaglandin (PG) E2 or I2 evokes a migraine-like headache in individuals with migraine (139). Interestingly, the migraine attack evoked by PGE2 occurred immediately after infusion in the majority of patients, in contrast to the 2–4-hour delay before the occurrence of migraine that was more commonly observed with PGI2 or with all other reported migraine triggers (140). PGs are synthesized from arachidonic acid by activated cyclooxygenase.

Elevated levels of PGE2, PGD2, and PGF2α in saliva have been reported in migraine patients during attacks, and these levels may be normalized coincident with headache relief (141,142). Levels of PGE2 and PGI2 have also been reported to be elevated in blood from the external jugular blood during migraine attacks (143). The efficacy of non-steroidal anti-inflammatory drugs as acute and preventive therapies and for migraine supports a role for PGs in migraine. Specific receptors for PGs, particularly PGE2 and PGEI2, are appealing targets for migraine therapy (139).

Migraine-associated sensory sensitivity

There is growing insight into the sensory sensitivity that is associated with migraine. Migraine pain continues to be worsened by light in patients in whom rod and cone damage cause blindness, indicating that there are alternative pathways for mediating light sensitivity in migraine, possibly a direct pathway from the retina to a region of the posterior thalamus that also responds to stimulation of the dura (144). These findings demonstrate the existence of non-trigeminal pathways that influence migraine pain.

The occipital cortex has also been shown to be hyperexcitable in association with migraine photophobia independent of headache. An $H2^{15}O$ PET study in migraineurs showed that low-intensity light stimulation activated the visual cortex during spontaneous migraine attacks associated with photophobia and after treatment with sumatriptan, but not during the attack-free interval (145). The thalamus may also play a key role in sensory sensitivity during migraine. Mechanical and thermal allodynia (the perception of ordinarily innocuous stimuli as uncomfortable) associated with migraine are associated with increased thalamic responses to sensory stimulation based on fMRI blood oxygen level-dependent imaging (102).

The migraine postdrome

A number of symptoms of a migraine attack may occur following resolution of a headache, also known as the 'postdrome' (24,146,147). These symptoms include tiredness, weakness, cognitive difficulties, mood change, residual head pain, lightheadedness, and gastrointestinal complaints. Some of these symptoms may become apparent upon treatment of headache, leading to the impression that they are an adverse effect of migraine therapy rather than a part of the attack (148). Functional imaging studies indicate that either hyperperfusion or hypoperfusion may persist beyond the headache phase, either with spontaneous resolution of headache or with successful treatment with sumatriptan (149). PET studies have shown that activation of the dorsolateral pons in non-trigeminal-triggered migraine persists after amelioration of headache with sumatriptan (101). Similarly, midbrain and hypothalamic activation, as well as increased light-induced activation of the visual cortex, may also persist- after headache relief (28,150). These observations clearly demonstrate that changes in brain activity may continue for extended lengths of time after either spontaneous or therapeutic resolution of headache.

Chronic changes with chronic headache

Structural and functional imaging studies indicate that migraine may be associated with long-lasting changes in regions of the brain that are involved in the processing and modulation of pain (98). These changes consistently include a decrease in gray matter volume in the anterior cingulate and insular cortex, and in some studies also include decreased gray matter volume in thalamus, orbitofrontal, prefrontal, and somatosensory cortex among other regions (151,152–154). In the majority of these studies the extent of gray matter decrease was correlated with the duration of the disorder. Some studies have also reported an increase in gray matter volume in the periaqueductal gray and in the dorsal pons in the brainstem (152). A decrease in gray matter volume has also been reported in similar regions in patients with chronic tension-type headache (155). Key questions regarding these morphological and functional changes include whether or not any are specific to headache, and whether they represent a cause or a consequence of chronic headache. A number of chronic pain syndromes other than headache are associated with similar changes in the structure and function of brain regions involved in nociceptive processing, suggesting that they may be a general response to pain rather than specific to migraine (156). The observation that some of the changes are reversible upon effective treatment of pain suggests that the changes are a response to pain rather than a cause of it (157,158). Regardless of what role they play in headache, however, it is clear that significant changes in brain structure may occur in the setting of headache disorders. These observations suggest that structural plasticity of the brain may accompany worsening or improvement of headache. This concept raises the speculative possibility that mechanisms of brain plasticity that are therapeutic targets for other neurological disorders such as stroke and neurodegenerative disorders could also represent targets for headache, particularly chronic headache.

Recent studies have also examined chronic changes in potential neurochemical mediators in patients with chronic migraine. Interictal levels of CGRP in peripheral blood have been reported to be significantly higher in patients with chronic migraine compared with healthy controls or those with episodic migraine, and CGRP levels were particularly increased in patients with chronic migraine who had a history of migraine with aura (159). These findings add to studies implicating CGRP in an acute migraine attack, and provide support for preventive therapies targeting CGRP and its receptor.

Cluster headache

While there is some overlap between mechanisms of cluster headache and those of migraine described above, cluster headache clearly involves distinct anatomical, neurochemical, and physiological features (see also Chapter 18). The prominence of cranial autonomic features in cluster headache indicates a greater role for the autonomic nervous system, particularly the sphenopalatine ganglion (160).

Another distinguishing feature of cluster headache is the involvement of the posterior hypothalamus as indicated by chronic changes in gray matter density, as well as functional activation during cluster attacks (161). A primary role for the hypothalamus in cluster headache is consistent with the circadian rhythmicity that is a common characteristic of the disorder. The responsiveness of cluster headache attacks to oxygen is another distinguishing feature. Rodent studies indicate that oxygen inhibits activation of the trigeminocervical complex triggered by parasympathetic stimulation but not by stimulation of meningeal afferents (162). This selective effect of oxygen on activation of brainstem pain processing neurons by a trigeminal autonomic reflex may be responsible for its specific efficacy as a therapy for cluster headache. A better understanding of the commonalities and differences between the mechanisms underlying cluster headache, migraine, other headache disorders, and pain

disorders in general has the potential to yield important insight into each of them.

Conclusion

The mechanisms underlying headache disorders are extraordinarily varied and complex. Given the heterogeneity of their clinical features, it is likely that distinct mechanisms are involved in different individuals with the same disorder. The processes involved in headache are unlikely to occur as a linear cascade of events, but rather as parallel and overlapping phenomena that occur as a consequence of diffuse alterations in chemical and physiological function. Advances in genetics, imaging, clinical neurophysiology, and pharmacology will help us to further unravel the specific mechanisms responsible for these common and disabling disorders.

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5

Headache in history

Mervyn J. Eadie

Introduction

Humans almost certainly experienced headaches in prehistorical times. The finding of human skulls from around 10,000 BC that contained apparent trepanning openings made during life has led to speculation that the operations may have sometimes been carried out for headache relief. However, the first reasonably definite surviving written record of human headache originated in Mesopotamia some six millennia ago.

Ancient times

Mesopotamia

In 1903, R. Campbell Thompson translated an eighth century BC Mesopotamian cuneiform text that dealt with material that he thought had originated around 4000 BC (1). Part of the material indicated a belief that headache arose from the influences of invisible supernatural beings, or powers (demons and evil spirits). Headache occurred unpredictably and followed courses ranging from the benign and self-limited to the lethal. Various spells and magic rituals for headache relief were described, and also temporary binding of the head.

Texts originating from the Sumerian city of Nippur between 2113 and 2038 BC also reflected a belief that demonic activities caused headache (2).

Egypt

From the middle of the second millennium BC onwards, various Egyptian papyri mentioned headache. They mostly considered the considerable variety of treatments proposed for the symptom. Certain Egyptian deities, for example the sun-god Ra, were stated to suffer headaches (3). It appears that headache was still being attributed to supernatural influences. There was no indication that varieties of headache were recognized. The symptom was treated with incantations and spells, while numerous substances of animal, vegetable, or mineral origin were applied locally to the head, for example catfish skull, fish bones, root of the castor oil plant, wormwood, and clay.

Israel

The Old Testament book of Kings II, Chapter 4 (c. 800 BC) describes how one morning the only son of a Sunammite woman went to his father in the fields, and cried out 'My head, my head!' The boy was taken back to his mother, sat on her knee, and died. The prophet Elisha was summoned, and seems to have resuscitated the boy, who was mentioned as being alive 7 years later (II Kings 8.5). The medical nature of this episode is uncertain, for example possibly childhood migraine, but obviously headache was known in ancient Israel.

India

Headache received mention at various places in the writings attributed to Charaka (probably 500–300 BC). Numerous possible causes of headache were mentioned, for example retained urine and faeces, sexual excess, drinking cold water, smoke exposure, and cloudy weather. Various remedies were described (4).

Greece

An ancient Greek myth described how the god Zeus experienced headache before his head split open to allow Athena to emerge. Thus, there was awareness of headache in Greek society well before the writings of Socrates, Plato, Aristotle, and Hippocrates (fourth and fifth centuries BC). One of the *Dialogues of Plato* contains Socrates' advice to Charmides concerning cure of his headache. It mentions that the attempt at cure should assess the whole body, not merely the affected part (5). Aristotle's *The History of Animals* (c. 350 BC) mentioned postpartum headache and a sense of darkness before the eyes (possibly migraine with aura). However, the main medically significant ancient Greek writings on headache are in the Hippocratic corpus, although they contain no consolidated account of headache, as such. In these accounts, supernatural causes of headache gave way to physical factors, for example wine drinking. There were observations on headache prognosis and treatment, for example dividing the vessel running vertically in the forehead to relieve pain at the back of the head. One of the later Hippocratic writings (6), not included in Adams' translation of the *Genuine Works of Hippocrates* (7), contained two very similar accounts of almost certain migraine with aura:

> Phoenix's problem: he seemed to see flashes like lightning in his eye, mostly the right. And when he had suffered that a short time, a terrible pain developed toward his right temple and then around his whole head and on to the part of the neck where the head is attached behind the vertebrae. And there was tension and hardening around the tendons. If he tried to move his head or opened his teeth, he could not, as being violently stretched. Vomits, whenever they occurred, averted the pains I have described, or made them gentler (6).
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> Smith WD. Hippocrates. Vol 7. Cambridge, Mass. Harvard University Press; 1994.

The Hippocratic writings mark the beginning of an acceptance, at least in Western medicine, that headache has physical causes. From here on, the present account deals only with headache not due to organic disease, i.e. primary headache. This avoids the need to consider the numerous individual diseases, which, taken collectively, still cause only a small minority of all headaches.

Early Christian era

There seems little evidence that distinct headache syndromes were recognized until the writings of Celsus in the early first century AD (8). Celsus described *cephalalia* (headaches of various patterns, sites, and prognoses) and *hydrocephalus* (headache associated with swelling of the scalp). He wrote a great deal about headache treatment, and there was even more in Pliny's *Natural History* (9) and in the great *Herbal* of Dioscorides (c. 40–90 AD) (10). In the second century surviving writings of Aretaeus (11), and the probably slightly later works of Galen, a classification of headache types appeared and was to endure for many centuries.

Aretaeus

In part of his lost writings, Aretaeus probably dealt with *cephalalgia*, a short-lived headache. Elsewhere, he distinguished it from *cephalaea*, chronic or recurrent headache, that, if strictly one sided, he termed *heterocrania*. His description of the latter suggests that it included both migraine and other one-sided head pains. Aretaeus based his interpretation of headache mechanisms on humoral pathology, not on supernatural influences, *cephalaea* being due to coldness and dryness. His recommendations for headache treatment involved correcting the postulated imbalance of the responsible humours by employing measures such as bleeding, cupping, enemas, or sternutatories (to promote sneezing).

Galen

Galen's (121–c. 200 AD) ideas on headache appear at various places in his *Omnia Opera* (12). He recognized *cephalalgia (dolor capitis)* and *cephalaea*, and at places seemed to regard *hemicrania* (Aretaeus' *heterocrania*) as a separate headache entity (a recognition usually attributed to Alexander of Tralles, c. 600 AD). Thus originated the triad of headache types, viz., *cephalalgia, cephalaea*, and *hemicrania*, that persisted in medical terminology for almost two millennia. Over that long period the terms were not always used consistently, and *cephalalgia* gradually subsumed the headaches originally termed *cephalaeas*. This venerable terminology does not fit particularly well with modern-day headache types. Thus, *hemicrania* would exclude migraine with bilateral headache, and includes one-sided headache due to organic disease. Galen recognized that external factors (e.g. heat, cold, inebriation, exercise) and internal disturbances (e.g. stomach disorders, uterine 'irritation', suppression of the menses) could cause headache, and described an extensive array of headache medications (in volume 12 of the *Omnia Opera* (12)).

Subsequent Byzantine medical writers (e.g. Caelius Aurelianus, Oribasius, Paul of Aegina, and Alexander of Tralles) added little of major conceptual importance to Galen's ideas, although some of their anti-headache pharmacopoeias were more extensive. They too employed humoral concepts of headache pathogenesis, sometimes with different details. However, in the general community, ideas of supernatural origins of headache lingered, with treatment attempts being directed accordingly, e.g. utilizing charms.

The Middle Ages

The medieval Arab physicians wrote on headache, but their ideas largely depended on Galen's concepts from long before. They employed the familiar triad of headache types, naming simple non- recurrent headache *seda*, continued bilateral or recurrent headache *bayzeh*, and recurring pulsatile one-sided headache *shaqhiqheh.* They understood that headache could arise from brain disease, systemic disorders, and psychological factors (13). Haly Abbas thought that headache originated either in the head itself, or in the stomach, and then affected the head via the agency of 'sympathy'.

There has been recent interest in the writings and illustrations of the medieval mystic abbess, Hildegard of Bingen (1098–1711). Charles Singer (14) suggested that the zig-zag patterns forming parts of her illustrations raised the possibility that she had experienced migrainous visual auras (**Figure 5.1**). If so, there seems no evidence that her writings had any contemporary impact on headache knowledge.

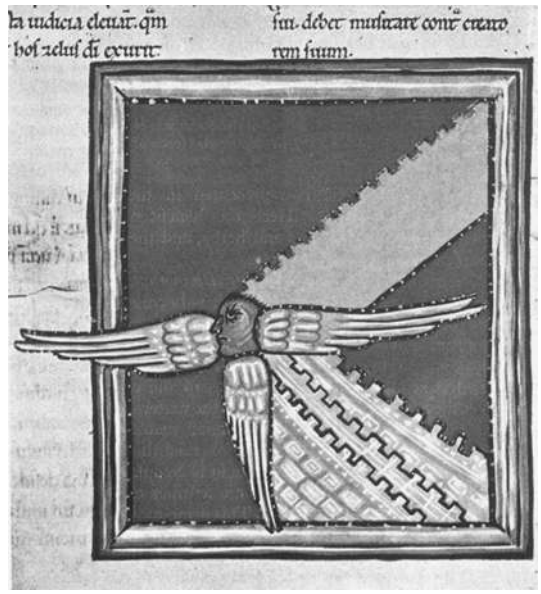


Figure 5.1 Illustration from Hildegard of Bingen's writings, showing a V shape with serrated edges resembling a migrainous visual aura phenomenon, but with a face and attached wings at the apex of the V. The original appeared in Hildegard's *Scivias* (c. 1180).

Reproduced from Singer C. The scientific views and visions of Saint Hildegard (1098–1180). In Singer C (Ed) *Studies in the history and methods of science*, Clarendon Press. 1917; pp. 1–55.

Fernel

In mid-sixteenth-century Paris, Jean Fernel (Fernelius) stated that all headache arose from the meninges, the headache features depending on the type of humour that impacted on these membranes (15). Sharp bilious vapours produced sharp bilious headache, cold phlegmatic humours heavy headache, and flatulence or less malign vapours, when insinuated between skin and pericranium or between skull and dura, caused tense headache. Distended pulsating arteries produced tight pulsatile headache. Such ideas about headache mechanisms might have provided a basis for a classification of headache types based on mechanism, but none appeared.

Despite such more scientific attitudes appearing, the majority of headache sufferers probably still held supernatural concepts regarding headache production. Thus, Martin Luther (1483–1546) attributed his headaches to the malice of the Devil (16).

The scientific revolution

At the end of the sixteenth century, Phillip Barrough (17), still heavily dependent on Galen, stated of *hemicrania* that: 'this griefe in English is called Migrime.' He described *cephalaea* in a way that strongly resembled (non-unilateral) migraine without aura, stating that it occurred more frequently in women because of their long hair.

Le Pois

In 1618, Charles Le Pois (Carolus Piso, 1563–1613), himself a headache sufferer (18), published ideas of headache pathogenesis resembling those of Fernel. Le Pois provided probably the first reasonably convincing description of a migraine aura to appear since the later Hippocratic corpus (c. 200 BC). This aura was a left-sided somatic sensory one. No associated visual phenomena were mentioned.

Wepfer

Later in the seventeenth century two major, near contemporaneous, authors wrote on headache, although the ideas of the Swiss, Johann Jakob Wepfer (1620–1695), appeared posthumously, in 1727 (19). Nearly 100 pages of Wepfer's *Observationes medico-practicae de affectibus capitis* were devoted to descriptions of individual instances of headache and his commentaries on their causes and mechanisms. Wepfer used the *cephalalgia, cephalaea, hemicrania* classification and dealt with a mix of primary and symptomatic headache entities. His Observation 54 described a *hemicrania* with a visual aura (moving objects resembling flies) that developed in parallel with the headache. Some of his 14 instances of *hemicrania* were due to detected organic disease. There was a possible account of trigeminal neuralgia. Isler (20) suggested that Wepfer's Observation 108 may have been an instance of subsequently so-called 'basilar artery migraine'. However, a previous hemiplegia in the sufferer raises suspicion that organic basilar artery disease was present. Wepfer provided no overview of headache mechanisms, but proposed that a chylous humour from the stomach could cause head pain that originated in the meninges, and that the pain of *hemicrania* was of vascular origin and due to defective serum, or overfilled vessels. He thus provided early descriptions of some headache entities and perceived a role for vascular events in *hemicrania* pathogenesis.

Willis

In his *De Anima Brutorum*, which appeared in 1672 (21), Thomas Willis (1621–1675) devoted two chapters to *De Cephalalgia,* words 'English'd' by Samuel Pordage in 1683 as 'Of the Headach' (**Figure 5.2**). The translation suggests that *cephalalgia* had become the general term for headache in everyday English. Pordage also rendered Willis' '*hemicrania*' as 'Meagrim'. Although physicians cherished the Latin headache terms for another couple of centuries, by the seventeenth century the ordinary Englishman seems to have recognized the distinctive features of the disorder called 'megrim'. The French laity spoke of 'migraine' as early as the twelfth century.

It is difficult to do justice to Willis' headache writings in a short space. They contain not only important original insights, but also apparent inconsistencies, and are based on Paracelsian iatrochemical thinking that does not equate readily with modern knowledge. Willis related sites of headache occurrence to the richness of the local innervation, and considered that headache originated in the meninges (in particular), pericranium, nerve 'coats', muscle bellies, and skin. In discussing what probably was migraine, he postulated that 'morbific matter' (circulating material of unspecified chemical nature) affected the meninges and their nerves to produce pain, with repeated chemical insults permanently altering the dura to cause chronic headache. Elsewhere Willis seemed to attribute headache to altered intracranial arterial blood flow, and explained localized headache and *hemicrania* by increased flow in individual arteries. Thus, it can be argued that Willis was the progenitor of both the neural and the vascular theories of migraine pathogenesis, although he wrote concerning headache in general.

Willis described a 'venerable matron' who, over more than 3 weeks, experienced daily head pain from around 4pm until midnight. She then slept, and woke well next morning to repeat the cycle of events. No further useful details were provided, but this may be an early record of cluster headache, although Koehler suggested that Nicholas Tulp had described a similarly possible example in 1641 (22).

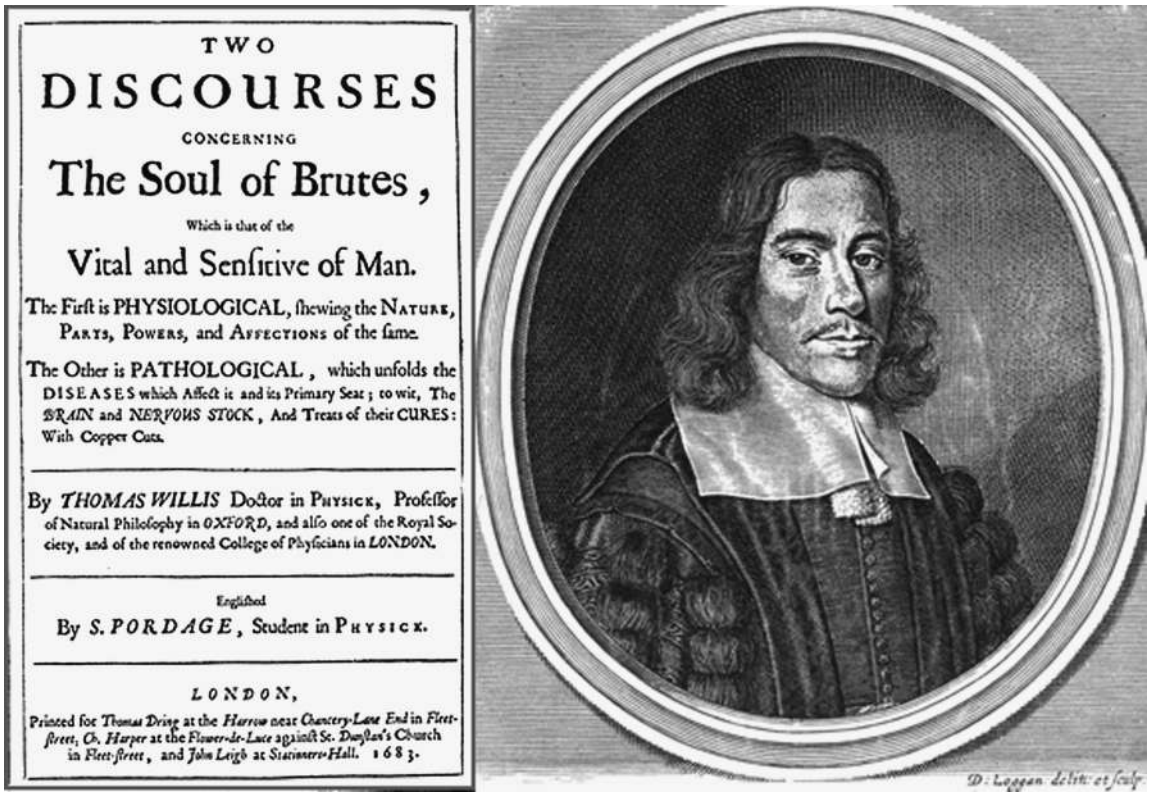
Sydenham

Thomas Sydenham (1624–1689), in writing on 'an affection called hysteria in women and hypochondriasis in men', described a very localized form of headache associated with vomiting (his *clavus hystericus*) (23). Authors as late as 1894 (24) continued to mention it (e.g. Tissot's (1778–1780) '*le clou*'). It may be the forerunner of today's 'nummular headache'.

The eighteenth century

As mentioned, eighteenth-century medical authors usually employed the *cephalalgia, cephalaea, hemicrania* terminology, with *cephalalgia* increasingly becoming the general term for headache, and *hemicrania* equivalent to the layman's 'migraine'.

In the latter part of the eighteenth century, major texts, such as Cullen's *First Lines of the Practice of Physic* (25), often contained no consolidated account of headache, while Boissier de Sauvages' attempted comprehensive classification of headache varieties in 1772 proved prohibitively complex (26).



TWO
DISCOURSES
CONCERNING
The Soul of Brutes,
Which is that of the
Vital and Sensitive of Man.
The First is PHYSIOLOGICAL, shewing the NATURE, PARTS, POWERS, and AFFECTIONS of the same.
The Other is PATHOLOGICAL, which unfolds the DISEASES which Affect it and its Primary Seat; to wit, The BRAIN and NERVOUS STOCK, And Treats of their CURES: With Copper Cuts.
By THOMAS WILLIS Doctor in PHYSICK, Professor of Natural Philosophy in OXFORD, and also one of the Royal Society, and of the renowned College of Physicians in LONDON.
Englished
By S. PORDAGE, Student in PHYSICK.
LONDON,
Printed for Thomas Dring at the Harrow near Chancery-Lane End in Fleet-street, Ch. Harper at the Flower-de-Luce against St. Dunstan's Church in Fleet-street, and John Leigh at Stationers-Hall. 1683.

Figure 5.2 The title page of Samuel Pordage's (1683) translation of Willis' *De Anima Brutorum* with Willis' portrait from the frontispiece of *The Remaining Medical Works of That Famous and Renowned Physician Dr Thomas Willis.*
Reproduced from Willis T. De anima brutorum quae hominis vitalis ac sensitive est. 1672.

Fothergill

The London Quaker physician John Fothergill (1712–1780) described the visual aura of his own migraine in a posthumous publication (27):

> It begins with a singular kind of glimmering in the sight; objects swiftly change their apparent position, surrounded with luminous angles, like that of a fortification. Giddiness comes on, head-ach and sickness.
>
> Fothergill J. Remarks on that complaint commonly known under the name of the sick headach. Medical Observations and Inquiries. 1784; 6:103–137.

After many centuries of silence since the later Hippocratic writings this was an early reappearance of mention of a migraine visual aura, although, according to Rucker (28), Vater and Heinicke had described an instance in 1723 that long went unnoticed.

In 1783 Fothergill (29) had also described 14 instances of 'a painful disorder of the face' in which:

> a pain attacks some part or other of the face, or the side of the head: sometimes about the orbit of the eye, sometimes the *ossa malarum*. sometimes the temporal bones, are the parts complained of. The pain comes suddenly, and is excruciating. It lasts but a short time, perhaps a quarter or half a minute, and then goes off; it returns at irregular intervals, sometimes in half an hour, sometimes there are two or three repetitions in a few minutes.
>
> Fothergill J. Of a painful affection of the face. Medical Observations and Inquiries. 1773; 5:129. Reprinted in Lettsom, J C. The works of John Fothergill MD. Vol 2. London. Dilly. 1783:179–189.

This has often been considered the first account of trigeminal neuralgia (*tic douloureux*), although, as often happens after a new disease entity achieves wider recognition, earlier reports are traced. Lewy (30) thought Avicenna (980–1036) may have described it as 'Levket', and noted an account of its occurrence in Johanes Lauentius Bausch (1605–1665), founder of the Imperial Leopoldian Academy for Natural Sciences. The English philosopher (and occasional physician) John Locke had recorded in his diary its probable occurrence in the Countess of Northumberland, wife of the English Ambassador to France, in 1677 (31,32).

Parry

In 1792 Caleb Hillier Parry, of Bristol, noted that compression of the carotid artery on the headache side afforded temporary pain relief (33), an observation subsequently proved to be important in identifying a role for vascular mechanisms in *hemicrania* and bilious headache. Actually, long before, Galen, in *De locis affectis*, noted that the now-lost works of Archigenes (late first or early second-century AD) mentioned that strong compression of blood vessels (presumably in the scalp) relieved headache (34). Parry (35) also described an episode of probable migraine with a visual aura followed by right upper limb and facial sensory symptoms, then inability to speak and mental confusion, culminating in headache.

Tissot

In the 1778–1780 period the first edition of Samuel Tissot's (1728–1797) highly influential *Traité des nerfs* appeared (36). In it, he dismissed in a few lines of text all varieties of headache except migraine.

He wrote at considerable length on the latter, providing the first major account of this particularly common type of headache that grasped the attention of the contemporary medical profession, at least in his native Switzerland and France. Tissot considered migraine and *hemicrania* synonymous, but pointed out that he had seen instances of non-unilateral headaches that were otherwise identical with migraine. He drew on the earlier literature and described the clinical features of the disorder much more comprehensively than hitherto, mentioning the presence of vision changes, scintillations, and bright lines during the attacks. He described in detail two instances of migraine with aura, one both visual and hemi-sensory, the other hemi-sensory only (probably Le Pois' case of 1618, mentioned earlier). Tissot did not comment that aura phenomena often preceded the headache, and that the pain was often pulsatile in character. He thought migraine arose from a stomach disturbance that affected the head by means of 'sympathy' mediated via nerve connexions (presumably the vagus). The sympathy affected the brain, causing nausea and perhaps vomiting, and reached trigeminal branches, mainly one supraorbital nerve, to produce unilateral headache. His ideas were derived from earlier writings and theoretical considerations, more than from experimental observation. Tissot's advice on treatment was mainly drawn from the literature, although he tended not to recommend over-vigorous measures.

Tissot's writings, given time for the medical profession to absorb their import and for the knowledge to spread into the lay community, seem to have awakened a surge of interest in headache, almost exclusively migraine. This began in the French-speaking world of the nineteenth century, and later extending into English-speaking and other nations. This interest is reflected in the appearance of etchings and cartoons such as those shown in **Figures 5.3 and 5.4**.

The nineteenth century

Migraine

Much nineteenth-century French-language publications concerning migraine, particularly the numerous theses, tends to be repetitive, although some new insights emerged. By the end of the century migraine was a generally accepted major headache entity. The more significant French work on migraine began with Piorry.

Piorry

In 1831 and again in 1835 Pierre-Adolphe Piorry (37) described in some detail his 'iridial' or 'ophthalmic' migraine, i.e. migraine with a visual aura. He suggested that *hemicrania* was a one-sided head neuralgia. Some initiating factor, probably ambient light, acted on the retina and iris diaphragm of the eye to alter local nervous activity. This alteration set the pupil into a state of oscillating constriction and dilatation that was responsible for producing a zig-zag pattern of light on the retina. The altered neural activity extended into trigeminal territory, causing a supraorbital neuralgia. He thus explained the pathogenesis of both the migraine visual aura and the unilateral headache. Spread of the abnormal neural activity to vagal and sympathetic innervated structures could produce nausea and vomiting. Piorry's was an ingenious, comprehensive, but highly speculative, hypothesis. Some four decades later, in 1875, Piorry (38) reiterated the idea, adding the suggestion that the connection between the vagus and the trigeminal nerves occurred through the spheno-palatine ganglion. Migraine was, for him, an 'irisalgia'.

In 1832 Jules Pelletan de Kinkelin published a modified neural type of hypothesis of migraine pathogenesis (39). He suggested that neural inputs from various peripheral organs whose dysfunction seemed related to the onset of migraine (the iris, stomach and uterus, and congested blood vessels) were transmitted through the brain to first-division trigeminal branches in whose territories of supply pain was experienced. The idea did not survive. Anatomical evidence of the proposed cerebral connections was lacking.

Seven years later, Louis-Florentin Calmeil (40) reversed the postulated sequence of neural events, hypothesizing that migraine arose from a brain disturbance that spread from its cerebral origin along anatomically verified nerve pathways to the trigeminal system and, mainly via the vagus, to abdominal organs. The Londoner Francis Anstie, in 1866, also considered migraine headache neuralgic in nature, but originating in trigeminal branches themselves (41).

Vascular hypotheses of migraine pathogenesis also appeared. Marshall Hall in 1849 suggested that peripherally initiated afferent nerve activity reflexly produced neck muscle spasm that obstructed venous outflow from the head (42). The consequent cranial venous congestion caused headache. In that same year Auzias-Turenne (43) postulated that mainly unilateral venous congestion in the cavernous sinus caused trigeminal nerve (first division) compression. This explained unilateral headache, with carotid artery pulsation within the sinus making the pain throb. Ophthalmic vein congestion caused reddening of the eye and possibly blurred vision, while jugular venous distension within the carotid sheath could compress the vagus nerve to produce nausea and vomiting. Turenne's was another ingenious idea that accounted for numerous clinical phenomena, but perished from want of confirmatory evidence of the postulated mechanism.

Du Bois Reymond

In 1861 a less speculative hypothesis appeared when Emil Du-Bois Reymond (1818–1896), the Berlin physiologist, published an analysis of his own migraine phenomena (44). He specified that his explanation did not necessarily apply beyond his personal situation, a stipulation largely ignored by those who cite his idea. The headaches in his right temple increased with each beat of his superficial temporal artery, the artery felt harder than its left-sided counterpart, his face was pale, and his right conjunctiva appeared slightly injected. Recently available knowledge of cervical sympathetic function allowed him to suggest that right-sided sympathetic overactivity caused his early symptoms, the basic disturbance being at the origin of the cervical sympathetic trunk in the upper thoracic spinal cord. Brown-Séquard almost immediately rejected this interpretation, arguing that cervical sympathetic excitation in animals did not appear to cause pain, and that, in his experience, migraine manifestations more often were consistent with cervical sympathetic paralysis (45). Möllendorf's clinical experience, described in a 1867 paper (46), supported Brown-Séquard's view. Two years later Jaccoud, to an extent, reconciled these apparently contrary neurovascular interpretations by proposing that during a migraine attack cervical sympathetic over-action might be followed by under-action (47). Then Eulenburg, in 1877, stated that there was no marked vasomotor change in some migraine attacks, and proposed that any rapid change in scalp arterial calibre might irritate nearby trigeminal nerve terminals to cause headache (48). The Cambridge academic P. W. Latham, in 1872 and 1873, had also suggested that initial cervical sympathetic overactivity in migraine attacks produced cranial vasospasm, the resulting brain ischaemia being responsible for

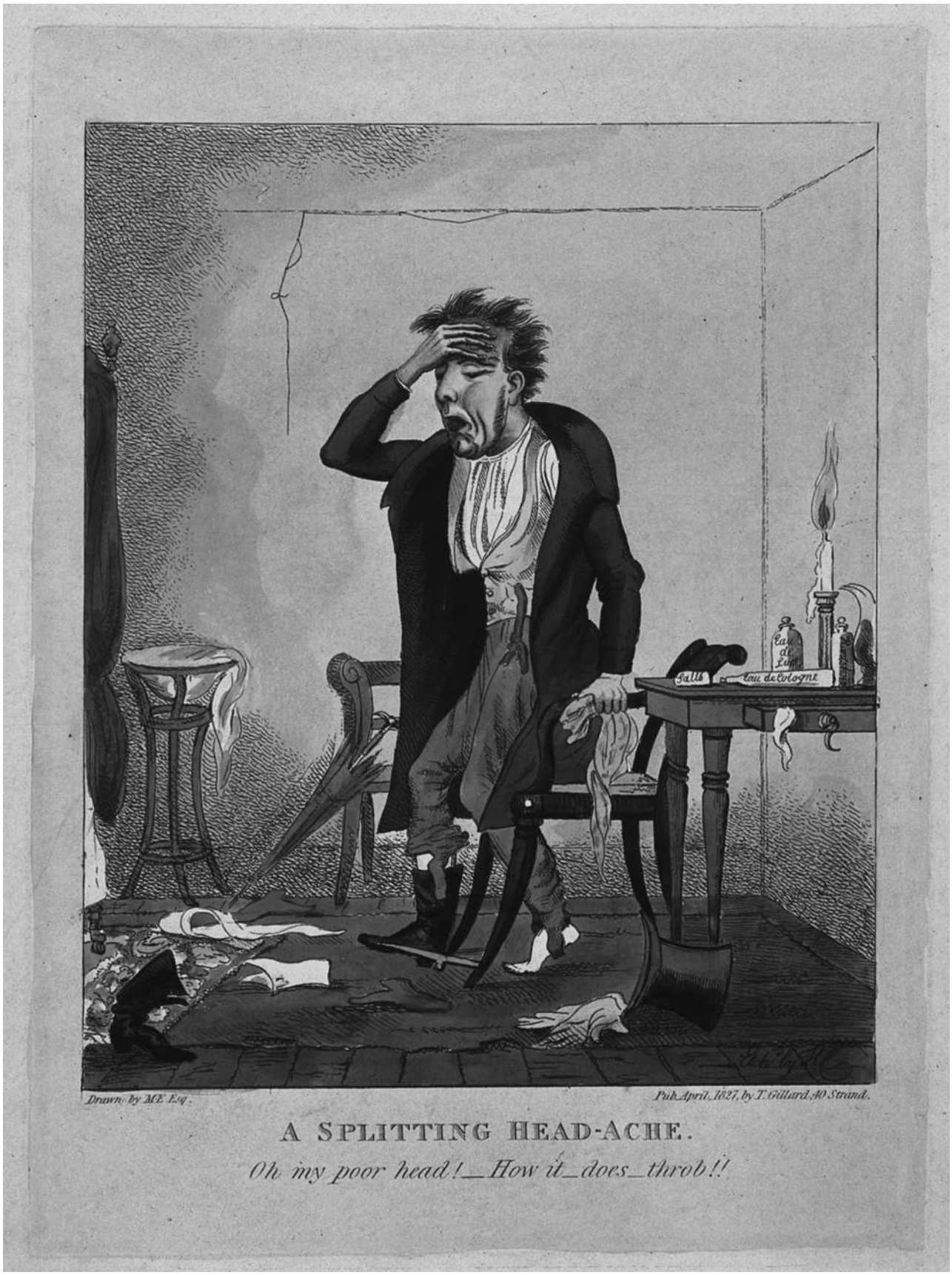
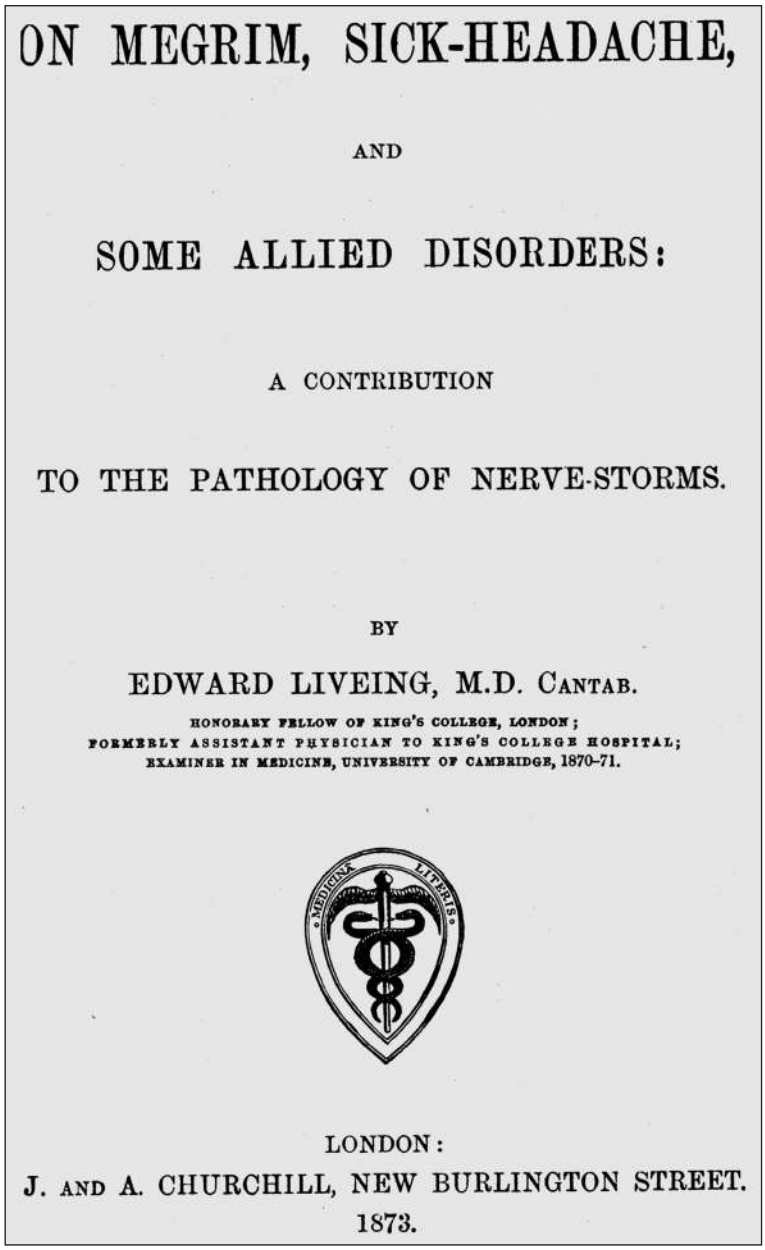


Figure 5.3. Etching of a man with a splitting headache.
Courtesy of the Wellcome Collection, Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0

Figure 5.4 Lithograph of a man whose headache was experienced as if his head was being repeatedly hammered by devils.
Courtesy of the Wellcome Collection, Attribution 4.0 International (CC BY 4.0), https://creativecommons.org/licenses/by/4.0



ON MEGRIM, SICK-HEADACHE,

AND

SOME ALLIED DISORDERS:

A CONTRIBUTION

TO THE PATHOLOGY OF NERVE-STORMS.

BY

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FORMERLY ASSISTANT PHYSICIAN TO KING'S COLLEGE HOSPITAL;
EXAMINER IN MEDICINE, UNIVERSITY OF CAMBRIDGE, 1870-71.

LONDON:
J. AND A. CHURCHILL, NEW BURLINGTON STREET.
1873.

Figure 5.5 The title page of Liveing's monograph on migraine.
Reproduced from Liveing E. On megrim, sick-headache, and some allied disorders: a contribution to the pathology of nerve-storms. London. Churchill; 1873.

any migraine aura that occurred (49,50). Subsequent sympathetic exhaustion produced headache as cranial arteries then dilated. The ideas of Latham, and before him, of Jaccoud, re-emerged three-quarters of a century later in the writings of Harold Wolff (51), who is now often credited with devising the vascular hypothesis of migraine pathogenesis.

Liveing

Almost simultaneously to Latham, Edward Liveing in 1873 wrote the great classic of migraine literature, a monograph *On Megrim, Sick Headache, and Some Allied Disorders* (Figure 5.5) (52). This work contained Liveing's clinical observations and a thorough and detailed literature review. Liveing wrote at a time when medicine was becoming increasingly aware of the existence of localized representation of function in the brain and proposed that migraine resulted from a 'nerve storm' or 'neurosal seizure' within the brain. Liveing postulated that his nerve storm could occur anywhere between the thalamus and the vagal nuclei in the brain stem. A thalamic discharge accounted for the visual aura, a vagal nuclear disturbance for nausea and vomiting, and a discharge in intermediate areas somehow explained the headache itself. Liveing's idea was developed before the course of the optic pathway beyond the thalamus was known.

Airy

In 1870 another Cambridge man, Hubert Airy (1838–1903), described his own migraine aura and illustrated its evolution (Figure 5.6) (53).

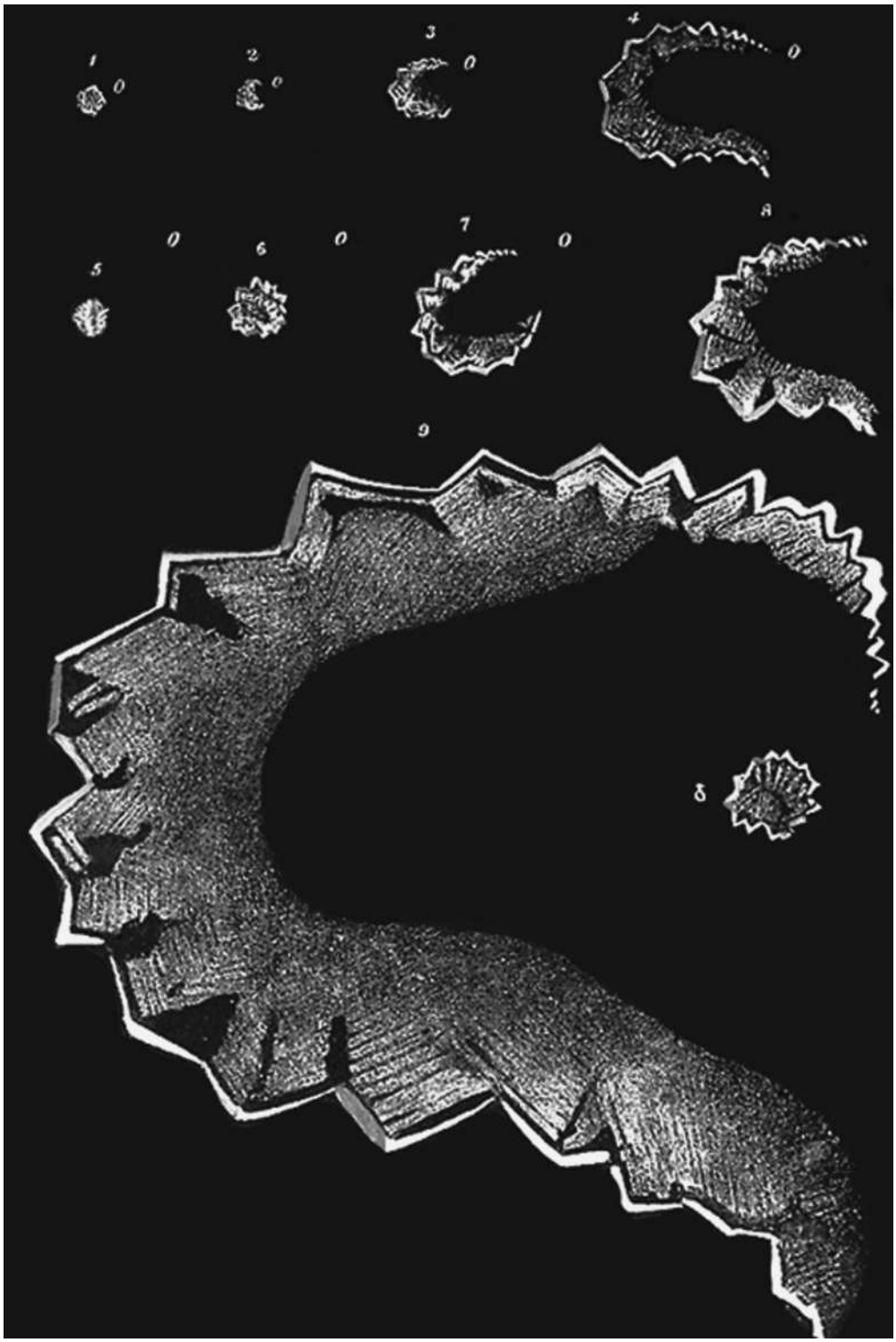


Figure 5.6. Hubert Airy's drawing of the evolution of his migraine aura from its beginning (top left corner).
Reproduced from *Philosophical Transactions*, 160, Airy H, On a distinct form of transient hemiopsia, pp. 247–264, 1870.

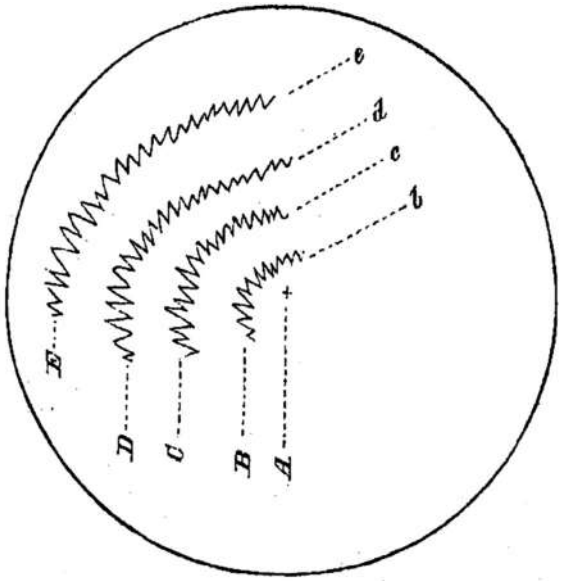


Figure 5.7 George Airy's drawings of the development of his scintillating scotoma.

Reproduced from *Philosophical Magazine*, 30, Airy GB, The Astronomer Royal on hemianopsy, pp. 19–21, 1865.

He reviewed the relevant literature and described the auras of a number of contemporary Fellows of the Royal Society, whether or not their auras were accompanied by headache. One of the Fellows was Airy's father, the British Astronomer Royal, Sir George Biddell Airy, who in 1865 had already illustrated the evolution of his visual auras (Figure 5.7) (54). The younger Airy did not propose a mechanism for the aura or headache, but posed questions for his readers that suggest that he believed the aura arose within the brain. His paper, more than the occasional earlier mentions of migraine auras in the late-seventeenth- and eighteenth-century literature, probably made English-language neurology as aware of migraine phenomena as the French literature already was. Indeed, a French librarian, Louis Hyacinthe Thomas, in 1887 authored a monograph on migraine in which he divided the topic into *migraine vulgaire* (common migraine, migraine without aura) and *migraine ophthalmique* (essentially, migraine with aura) (55). This classificational distinction remains widely accepted.

Liveing's domestic neighbour William Gowers (1845–1915), in volume 2 of his great *Manual of Diseases of the Nervous System*, which first appeared in 1888, provided a wonderfully clear, critical, and comprehensive account of migraine phenomena (56). Gowers believed that migraine originated in the cerebral cortex, but was circumspect regarding the initiation of the postulated cortical disturbance, possibly knowing that his London colleague Sidney Ringer in 1877 had suggested that migraine was not due to Liveing's 'nerve storms', but resulted from a local loss of cerebral cortical 'resistance' (a concept akin to loss of inhibition) (57). In his 1895 Bowman Lectures (58), Gowers discussed migraine visual auras in considerable detail and illustrated their appearances with drawings made by a patient (Figure 5.8), and also by Hubert Airy (Figure 5.9).

Non-migrainous headache

By the late nineteenth century, migraine was reasonably firmly established as a distinct headache entity and it was increasingly accepted that migraine headache did not have to be strictly one-sided. The old *cephalalgia, cephalaea, hemicrania* classificational triad was proving increasingly unsatisfactory in the light of growing knowledge of the pathological basis of disease. Various new headache classifications were proposed, partly to accommodate the residue of headache patterns that remained after migraine was excluded. Some of these classifications were based on presumed headache cause, or mechanism or site of pain origin. Entities such as rheumatic, neuralgic, and congestive headache were proposed, but no headache classification achieved any sustained popularity.

The twentieth century

An important new headache syndrome, later termed cluster headache, was recognized early in the twentieth century. From mid-century onwards, there were great advances in knowledge concerning migraine and reasonably satisfactory headache classifications appeared (59–61).

Cluster headache

In 1926 Wilfred Harris (1869–1960) described 'migrainous neuralgia' in his monograph *Neuritis and Neuralgia* (62). Some of his case histories probably represented migraine. Others were instances of 'periodic migrainous neuralgia' or what he later called 'migrainous (ciliary) neuralgia' (63). The clinical features of this disorder, viz. attacks of localized unilateral anterior head pain with a particular set of accompaniments and a tendency to recur in periodic bouts, were those of what was later termed 'cluster headache'.

Apparently initially unaware of Harris' work, Bayard Horton (1895–1980), from 1939 onwards, described 'histaminic cephalalgia'(64). Its clinical features also were those of cluster headache. Horton erroneously believed that this disorder responded specifically to courses of histamine injections. It was for Kunkle and his colleagues in 1952 to describe additional cases and coin the name 'cluster headache' (65). Once the entity was recognized, earlier instances were traced in the literature, including those mentioned previously in this chapter, and ones described by von Swieten in 1745 (66), Whytt in 1768 (67), and Morgagni in 1779 (68). Relatively recently, what could be considered cluster headache variants have been recognized and embraced in a designation of trigeminal autonomic cephalalgia (69).

Migraine

In the early decades of the twentieth cntury new hypotheses appeared accounting for the pathogenesis of the migraine attack. Some were vascular or neural-type hypothesis variants. Others invoked novel factors such as choroid plexus herniating into and obstructing a narrow foramen of Monro (70), episodic brain swelling (71), pituitary swelling (72), allergy (disproven in the case of milk by Loveless (73)), and errors of refraction (74), while Freud devised a psychodynamic interpretation (75). None of these ideas proved persuasive, and major progress did not occur until the work of Harold Wolff, in New York, appeared mid-century.

Figure 5.8 Drawing made by William Gowers' patient Beck of a scintillating scotoma in the upper part of his visual field.
Reproduced from Lectures on Diseases of the Nervous System. Second Series. Subjective Sensations of Sight and Sound, Abiotrophy, and Other Lectures. By Sir William Gowers, M. D. (Philadelphia: P. Blakiston's Son & Co., 1904). *American Journal of Psychiatry*, 61(2), pp. 372–373.

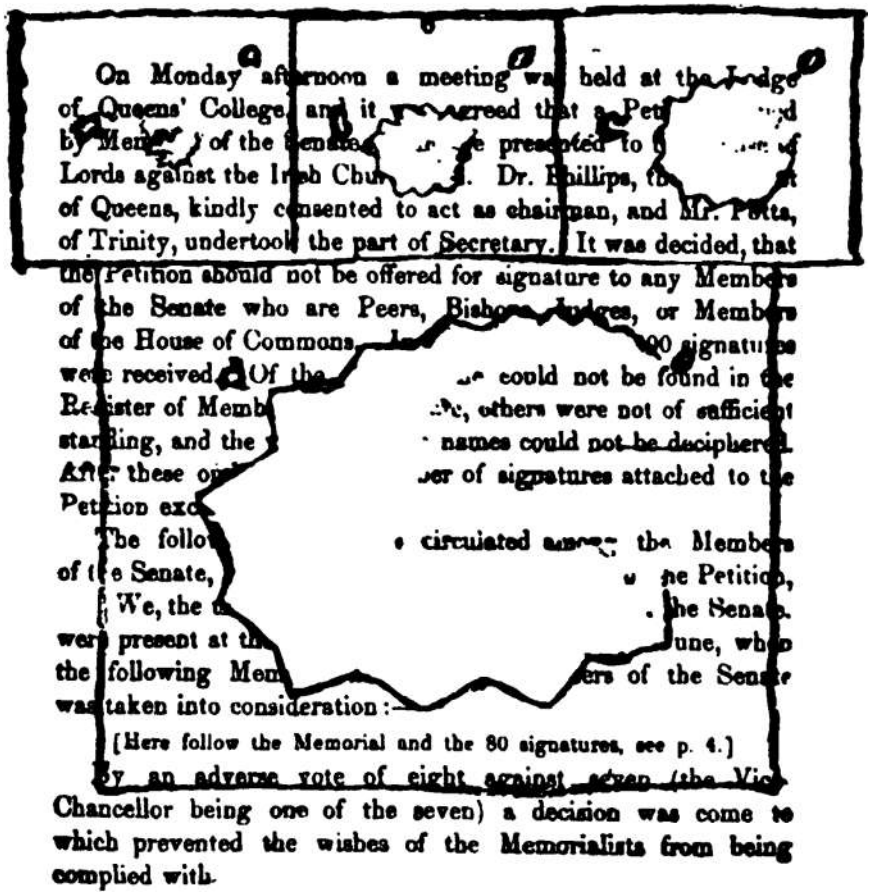
Wolff

A sustained program of experimental studies, many of them in human migraine sufferers, provided Harold Wolff (1898–1962) with a scientific basis from which to re-enunciate ideas proposed on much less adequate data by Jaccoud and Latham nearly a century before. Local cerebral arterial constriction produced the migraine aura and, as the constriction passed off, arterial dilatation caused the headache. To this Wolff added a significant new idea, viz. that the pain from the vasodilatation triggered painful contraction of head and neck muscles, a second pain-producing mechanism in the attacks. Wolff's contribution to knowledge about headache, and particularly migraine, was amassed in the second, posthumously published, edition of his *Headache and Other Head Pain* (51).

Following Wolff's work, knowledge about headache and headache mechanisms and treatment grew apace. Perhaps the main advances in relation to migraine arose from recognition of the phenomenon of cortical spreading depression by Leão in 1944 (76), and identification of the roles of serotonin and other neurotransmitters in the pathogenesis of the disorder. These advances are too recent for their consequences to be fully worked out and their historical significances appropriately assessed.

Tension headache

The numerous sufferers of primary non-migrainous headaches seemed largely to escape sustained medical interest in the earlier part of the twentieth century. Shortly after the end of World War II an entity of tension headache began to be mentioned in the medical literature. The origin of the concept is difficult to trace. The term may have been used informally by physicians before it began to appear in print with its present meaning (earlier, 'tension headache' had occasionally referred to headache associated with high arterial tension, i.e. raised blood pressure). Early accounts suggested that tension headache arose from psychological factors (77,78). Wolff (51) thought that the pain was produced by neck and


On Monday afternoon a meeting was held at the Lodge of Queens' College, and it was agreed that a Petition, to be presented by Members of the Senate to the House of Lords against the Irish Church Bill. Dr. Phillips, the President of Queens, kindly consented to act as chairman, and Mr. Potts, of Trinity, undertook the part of Secretary. It was decided, that the Petition should not be offered for signature to any Members of the Senate who are Peers, Bishops, Judges, or Members of the House of Commons. [illegible] 900 signatures were received. Of these [illegible] could not be found in the Register of Members, others were not of sufficient standing, and the [illegible] names could not be deciphered. After these [illegible] number of signatures attached to the Petition exceeded [illegible]

The following [illegible] circulated among the Members of the Senate, [illegible] the Petition, [illegible] the Senate.

We, the [illegible] were present at the [illegible] June, when the following Members of the Senate was taken into consideration:—

[Here follow the Memorial and the 80 signatures, see p. 4.]

By an adverse vote of eight against seven (the Vice-Chancellor being one of the seven) a decision was come to which prevented the wishes of the Memorialists from being complied with.

Figure 5.9 Another of Hubert Airy's unpublished drawings of the evolution of one of his migraine auras.
Reproduced from Lectures on Diseases of the Nervous System. Second Series. Subjective Sensations of Sight and Sound, Abiotrophy, and Other Lectures. By Sir William Gowers, M. D. (Philadelphia: P. Blakiston's Son & Co., 1904). *American Journal of Psychiatry*, 61(2), pp. 372–373.

scalp muscle tension. Aring (79) believed that tension headache had earlier been called indurative, nodular, myalgic, or rheumatic headache. Currently, the headache mechanisms involved and the limits of the entity do not seem adequately understood.

Headache treatment

The account in this chapter contains little regarding headache treatment. This is not because there was little medical interest in the matter but because, over the many centuries, there had been a vast array of chemical substances administered locally, orally, rectally, intranasally, or systematically, and various physical manipulations of various degrees of violence employed to relieve headaches or prevent further attacks, but none had achieved any consistent or specific benefit. This situation altered when the ergot alkaloid derivative ergotamine came into use in the 1920s (80), although it had been available, unidentified, in ergot extracts since 1868 (81). In the 1970s part of the structure of the ergotamine molecule provided a basis for synthesizing a number of migraine-specific triptan derivatives (82).

Conclusion

The recorded saga of the human encounter with headache is already a lengthy one, and also one unlikely to be near its end.

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PART 2
Migraine

6. **Migraine: clinical features and diagnosis** *61*
   Richard Peatfield and Fumihiko Sakai
7. **Migraine trigger factors: facts and myths** *67*
   Guus G. Schoonman, Henrik Winther Schytz, and Messoud Ashina
8. **Hemiplegic migraine and other monogenic migraine subtypes and syndromes** *75*
   Nadine Pelzer, Tobias Freilinger, and Gisela M. Terwindt
9. **Retinal migraine** *92*
   Brian M. Grosberg and C. Mark Sollars
10. **Migraine, stroke, and the heart** *98*
    Simona Sacco and Antonio Carolei
11. **Non-vascular comorbidities and complications** *110*
    Mark A. Louter, Ann I. Scher, and Gisela M. Terwindt
12. **Migraine and epilepsy** *120*
    Pasquale Parisi, Dorothée Kasteleijn-Nolst Trenité, Johannes A. Carpay, Laura Papetti, and Maria Chiara Paolino
13. **Migraine and vertigo** *128*
    Yoon-Hee Cha
14. **Treatment and management of migraine: acute** *138*
    Miguel J. A. Láinez and Veselina T. Grozeva
15. **Treatment and management of migraine: preventive** *152*
    Andrew Charles and Stefan Evers
16. **Treatment and management: non-pharmacological, including neuromodulation** *165*
    Delphine Magis

6

Migraine

Clinical features and diagnosis

Richard Peatfield and Fumihiko Sakai

Introduction

Headache is by far the commonest presenting symptom in neurological clinics, and the idea is gaining popularity that the vast majority of such patients have migraine, be it mild or severe, with or without an aura. In assessing such patients, the clinician has two principal tasks—to ensure that there is no alternative explanation for the headache requiring specific treatment, and to assess the extent to which the headache is disrupting the patient's life and work in order to offer appropriate abortive medication or preventative treatment. Imaging and appropriate blood tests may be absolutely necessary to exclude other conditions, but the vast majority of patients seen in the neurology clinic with a long history of typical migraine and no physical signs on examination do not need any investigation. There is as yet no test for migraine, which has to be diagnosed from a typical history and negative investigations for alternatives when thought necessary.

The International Classification of Headache Disorders (ICHD) is intended to standardize the diagnostic criteria for headache disorders (1–3). They are also of some value in attempting to make the diagnosis of migraine more evidence based. In routine clinical practice, however, clinicians must have discretion in interpreting these criteria, and it is often appropriate to treat an atypical patient for migraine once realistic alternative diagnoses have been excluded.

Gender ratio

Migraine is predominantly a disease of women—most population-based epidemiological series suggests a ratio of 2–3:1 (4). Migraine is actually commoner in young boys than young girls, and the vast majority of women develop migraine at or soon after puberty. The incidence of new cases of migraine in males rises steadily at least until the 30s, whereas there is an unequivocal peak in women (4–7). Most migraine will have revealed itself by the age of about 30 in women and 40 in men, and it is appropriate to undertake more investigations in new cases of headache in patients older than this.

Frequency

The frequency of migraine is very variable, and is necessarily dependent on the source of the patients. Some have only one or two attacks per year, and will only rarely see the need for medical advice. The majority of patients with episodic migraine seen in a typical neurology clinic have between one attack every 2 months and two attacks weekly (8). It has recently become accepted that headache more frequent than this can still be migrainous ('chronic migraine') (4,9–11). In most cases episodic attacks gradually become more frequent, and this apparent 'transformation' can be explained by, for example, the overuse of potentially addictive analgesics such as codeine or triptans (12,13), female hormones such as the contraceptive pill or hormone-replacement therapy, or a depressive state. Recent epidemiological studies do suggest, however, that there are also patients with chronic migraine that seems to occur spontaneously without these exacerbating factors (11). Other risk factors for chronic rather than episodic migraine include a high body mass index, a lower level of education, and smoking (11).

Duration

The duration of migraine is equally variable. It can be as short as 1 hour in young children, although the majority of adult patients with migraine have headaches lasting at least 4 hours when untreated, and many last rather longer. ICHD-3 specifies that a typical migrainous headache lasts for 4–72 hours (untreated or unsuccessfully treated). The patient often describes the pain being situated in only one part of the head at the onset of the attack, and shifting to another part of the head as the attack evolves. Very short, well-localized pains lasting no more than a few seconds—'jabs and jolts', or 'ice pick pains' (14), are seen in patients often with a personal or family history of migraine, and should be considered migrainous in aetiology. Little treatment for these may be required.

Location

In about 60% of cases the headache of migraine is unilateral, usually hemicranial, although the pain may be confined to only one part of the head such as the left frontal or right temporal regions (8,15). Most patients will describe at least a minority of attacks occurring in a symmetrical position on the other side of the head and, as already mentioned, some pains can switch sides during an attack. The use of unilaterality as a diagnostic criterion for migraine makes assessment of this in large populations difficult, but it must be borne in mind that at least 40% of patients with unequivocal migraine have bilateral headache (8).

Undue scalp sensitivity ('allodynia') is experienced by over 60% of migraine patients (16). It usually starts about an hour after the onset of the headache, and there is evidence that the response of the headache to triptans is less good if treatment is delayed until after this time (17).

The pain is characteristically throbbing or pulsating, and worsened by physical activity, such as climbing stairs (8,15). Nausea and vomiting, the latter occasionally profuse, are again a diagnostic criterion for migraine; about 90% of patients are at least nauseated and 50% have vomited (8,15).

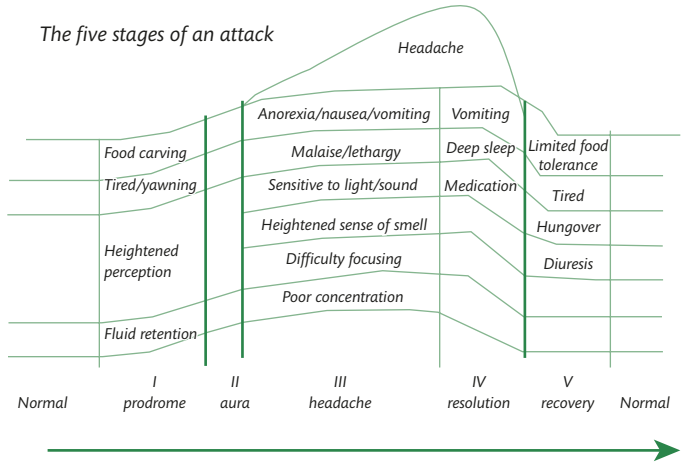

Figure 6.1 Pathophysiology of migraine.
Reprinted from *The Lancet*, 339, Blau JN, Migraine: theories of pathogenesis, pp. 1201–1207. Copyright (1992), with permission from Elsevier. DOI: https://doi.org/10.1016/0140-6736(92)91140-4.

Early premonitory symptoms

Many patients have vague and non-specific symptoms preceding the onset of more overt migrainous ones with or without a typical aura (18). These can include an ill-defined feeling of well-being, as well as yawning, thirst, fatigue, dizziness, and muscle aching. In a study of 97 patients given electronic diaries, Giffin et al. (19) demonstrated that 72% had some type of premonitory symptom, most commonly fatigue, poor concentration, and a stiff neck. Yawning, irritability, and emotional changes were also common, as well as the photophobia, phonophobia, and nausea that are considered part of the headache phase. These symptoms usually lasted less than 12 hours, although they were occasionally much longer (20). The symptoms at the end of a migraine attack often seem to 'mirror' those of the premonitory symptoms (see **Figure 6.1**) (21).

Aura symptoms

Perhaps 30% of population-based series of migraine patients experience aura symptoms of some kind (6,7,22). Auras usually precede the headache, although they can occur during it, and very occasionally a patient will describe repeated auras during a single headache (23). Migraine aura may be associated with a headache that does not fulfil the criteria used for migraine without aura (24); a small but definite minority of patients experiencing auras have no headache at all (25). Many of these are older patients who have had migrainous headache with preceding aura throughout their lives, and the headache has faded as they grow older while the aura has remained unchanged. There are other patients who present in later life with aura symptoms alone (26,27)—while many are typical, it is not always straightforward to distinguish all of these symptoms from those of transient ischaemic attacks (25), as is discussed in the section 'Sensory aura'.

Visual symptoms

Many of the earliest descriptions of migrainous aura phenomena were published by articulate migraine sufferers, many themselves medically qualified. These include Hubert Airy (28), Karl Lashley (29), Walter Alvarez (30), and Edward Hare (31). There is an excellent account in the book by Oliver Sacks (32). It is generally held that photophobia and blurring of vision are not wholly typical migrainous aura symptoms, and should not be labelled as such. Some patients complain of persistent visual afterimages or disturbances of the visual field akin to a 'broken windscreen' or a 'wet windscreen', while others have scotomas, or visual loss with or without a bright zigzag disturbance sometimes in a curve, usually on the temporal side of the field. This is believed to reflect the way visual cortical cells are arranged to respond to the orientation of an object seen. In many cases the visual disturbance moves across the visual field from close to the fixation point towards the periphery over 20–40 minutes (22,28,33). Very rarely it is apparent that this disturbance has migrated out of the visual areas of the brain completely, as the patient goes on to develop dysphasia first and then even a sensory disturbance in a sequence reflecting the location of these areas within the cerebral cortex. This wave of malfunction is followed by a further wave in which normal cerebral function and normal vision is restored. It is unusual but not impossible for a second wave to follow the first (see **Figures 6.2 and 6.3**).

Lashley (29) and Peter Milner (34) calculated that the disturbance runs across the cerebral cortical surface at a rate of 2–3 mm per minute, which is the strongest evidence that the spreading depression phenomenon described by Aristides Leao (35) is the cause of this. The likely mechanism of the aura is discussed by Whitman Richards (36), by Andrew Charles and Serapio Baca (37), and elsewhere in this book.

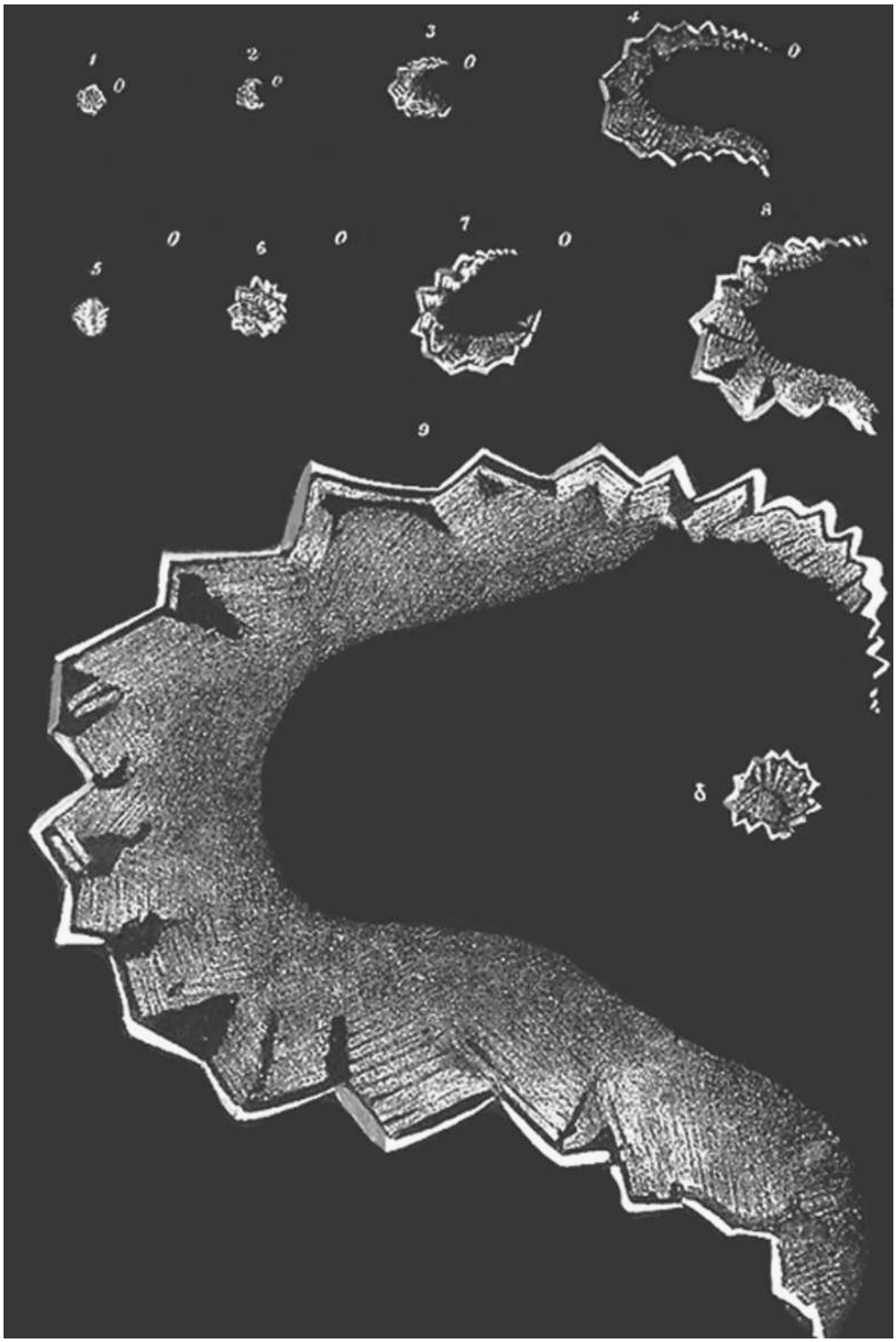

Figure 6.2 The visual aura drawn by Hubert Airy in 1870.
Reproduced from *Philosophical Transactions of the Royal Society*, 160, Airy H, On a distinct form of transient hemiopsia. pp. 247–264,1870.

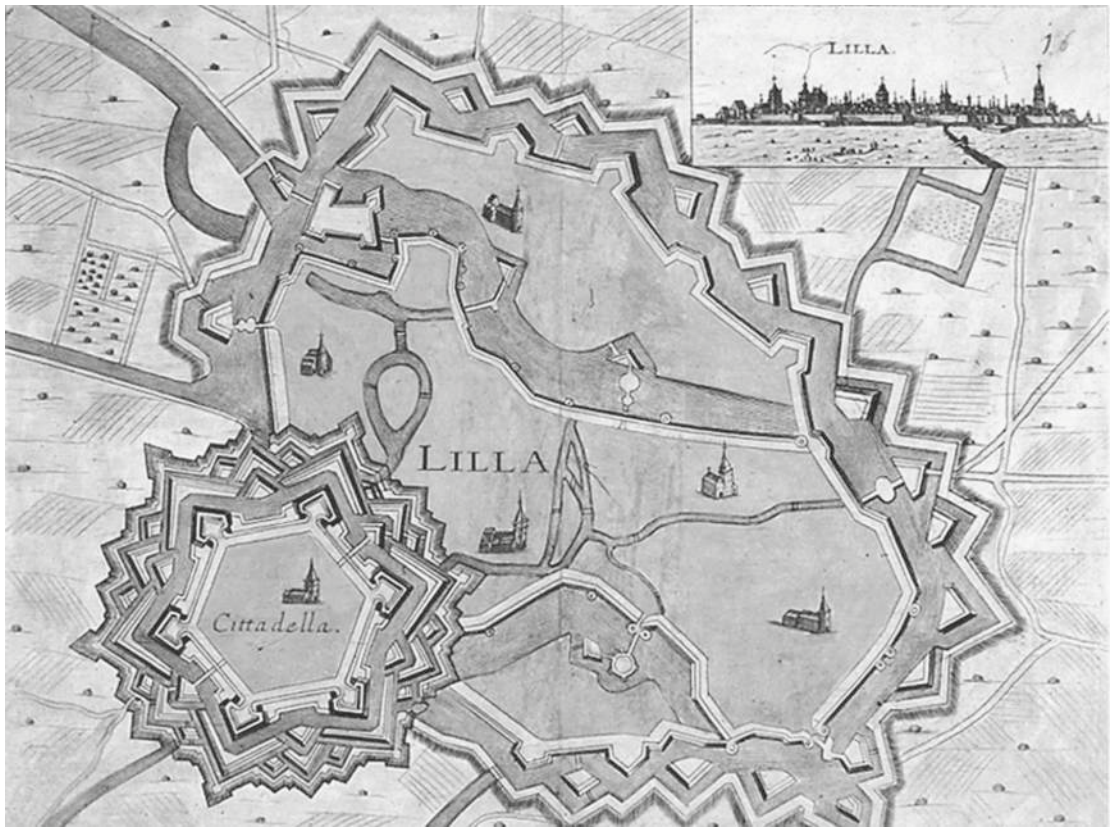

Figure 6.3 Map of Vaubon's new fortifications of the city of Lille.
Galeazzo Gualdo Priorato's *Teatro Del Belgio*, 1673.

Sensory aura

Many patients complain of paraesthesiae or numbness, most commonly in the parts of the body most heavily represented on the cortex—the lips, the face, and the fingertips. It is typical and almost pathognomonic of migraine that the sensory disturbance should migrate, taking perhaps 20–30 minutes to pass from the shoulder to the fingertips or vice versa. The symptoms of transient ischaemic attacks, in contrast, usually appear all at once and the vast majority of these last only a few minutes before resolving in a comparable manner.

Speech disturbances, including expressive and/or receptive dysphasias and paraphrasia are also commonly found. They usually also last for 20–40 minutes before resolving. Dysarthria can also occur.

Motor disturbances are rather rarer, with the exception of those seen in familial hemiplegic migraine (see Chapter 8) in which weakness can be the predominant symptom, although sometimes this is preceded by visual or speech disturbances (38). It has been argued that the motor cortex is separated from the parts of the brain most commonly affected by migraine by the Sylvian fissure, which seems to have an inhibitory effect on the disturbance passing across the brain surface. That the motor and sensory cortices are supplied by the middle cerebral artery and the visual cortex by the posterior cerebral artery, while migraine is most commonly seen in the visual, speech, and sensory cortices, has to be evidence that aura symptoms are not triggered by disturbances in flow within major blood vessels.

Transient global amnesia is much commoner in patients with a history of migraine (39). The memory disturbance usually lasts for several hours, which is longer than a typical aura and the attacks only rarely occur more than once in a lifetime. Visual hallucinations and confusion have been recorded (40), and even olfactory hallucinations (41). Vertigo as a symptom of migraine is dealt with in Chapter 13—whether there is a genuine constellation of posterior fossa symptoms that can be entitled vertebrobasilar migraine is problematic, and this term has now been replaced by 'migraine with brainstem aura' in ICHD-3, as involvement of the basilar artery is unlikely.

Many patients have more than one migrainous symptom (22,42), the commonest combination being visual and sensory symptoms. It has been recognized for a long time that patients can develop dysphasia at the same time as paraesthesiae and numbness in the non-dominant arm, which suggests that the neurophysiological disturbance can occur simultaneously in both hemispheres, albeit in a patchy manner. There is no clear relationship between the lateralization of the aura symptoms and the lateralization of the subsequent headache, which seems to be randomly distributed at least in many series (43). This certainly makes it difficult to offer a pathogenetic mechanism of migraine that relates the neurophysiological

disturbance of the presumed spreading depression in the cortex to a painful vasodilatation of the meninges overlying the cortex on the same side.

Specific migrainous syndromes, including hemiplegic migraine, both familial and sporadic, ophthalmoplegic migraine, and retinal migraine are covered elsewhere in this book (see Chapters 8 and 9).

The long-term prognosis

Migraine has a gratifying tendency to improve as the patients grow older. Many women, especially if their attacks have been linked to the menstrual cycle, find that they fade after the menopause, particularly if they are able to avoid hormone-replacement therapy. This is supported by cohort-based follow-up studies of migraine patients over many years, but the phenomenon is less easily demonstrated in epidemiological studies done at a fixed point in time, which suggests that there may be as many women who start at the menopause as there are those whose headaches settle down. The prevalence in older men, in contrast, is certainly lower than in younger men (44). It is often possible to withdraw prophylactic medication from patients as they grow older.

Complications of migraine

ICHD-3 lists four complications of migraine including status migrainosus, persistent aura without infarction, migrainous infarction, and migraine aura-triggered seizure.

Death in a wholly typical attack is exceptionally rare. The risk of ischaemic *stroke* in migraine is covered in Chapters 3, 10, and 37. All neurologists would be well advised to investigate any patient presenting with a permanent deficit after a typical migrainous attack with great care, to exclude cerebrovascular disease and cardiac disease, and particularly a persistent foramen ovale, as these seem to have an association with migraine with aura (45). It is only exceptionally that wholly uncomplicated migraine is followed by a permanent deficit. Haemorrhagic stroke is very rare but has been described (46). The association of migraine with *epilepsy*, and abnormalities of the cerebrospinal fluid are, likewise, covered elsewhere.

Conclusion

Migraine is a clinical diagnosis, and is perhaps the disease most clearly diagnosed by the history and examination, and not by investigation. There is an extraordinary variety of focal symptoms, as well as degrees of distress, which must be carefully evaluated before recommending treatment.

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7

Migraine trigger factors

Facts and myths

Guus G. Schoonman, Henrik Winther Schytz, and Messoud Ashina

Introduction

In second-century Rome, Galen of Pergamon suggested that migraine was triggered by yellow bile irritating the brain and meninges (1). Today, atmospheric, nutritional, hormonal, physiological, and pharmacological triggers are suspected, and have been investigated in numerous clinical studies. A trigger for migraine is any factor that upon exposure or withdrawal can lead to the development of a migraine attack (2). According to the International Headache Society (IHS) (3), trigger factors increase the probability of a migraine attack usually within 48 hours. A trigger factor is not regarded as a necessary causative agent in migraine and therefore the presence of a trigger factor may not always induce an attack and patients may have attacks without trigger. The majority of studies on trigger factors are retrospective surveys hampered by recall bias, multiple significance errors, and questionnaire design, which may explain differences between studies. There is only a limited number of prospective studies and these show conflicting results. In this chapter we will present and describe the present knowledge on migraine triggers, highlighting both facts and myths. In addition, we will discuss the clinical implications of identifying triggers, and whether there is any rationale for avoidance of triggers, which has been a classic strategy and recommendation for migraine treatment (4–6).

Atmospheric trigger factors

In this section we will only briefly summarize the findings regarding weather and migraine, as Chapter 54 deals with the relation between weather and headache (including migraine) in greater detail.

In short, many patients have the impression that changes in the atmosphere are able to trigger a migraine attack. Retrospective questionnaires showed that between 7% and 52% of migraine patients identified weather changes as a possible trigger factor (7). These questionnaire studies, however, are hampered by a variety of bias (8). Prospective studies, combining objective weather data from meteorological institutes with information from headache diaries or visits to the emergency room for migraine, showed no positive associations (9–11). Other studies found a triggering effect for temperature and relative humidity (11,12). It seems that there is a subgroup of migraine patients that might be susceptible to changes in weather (13).

Food and migraine

Between 10% and 50% of migraine patients are convinced part of their migraine attacks are triggered by certain food products (14). Based on retrospective questionnaires, a long list of possible migraine triggers has been formulated (Table 7.1). Among the most frequently mentioned products are alcohol (including wine), cheese, and chocolate, as well as withdrawal of caffeine and missing a meal. Prospective studies in which the intake of food and the occurrence of migraine attacks are scored independently using diaries are scarce. A large Austrian study included 327 migraine patients and assessed several potential trigger factors on a day-to-day basis. In that study the effect of nutritional factors was very limited. In fact, the consumption of beer even decreased the risk of getting a migraine attack (15).

Provocation trials in migraine

So far three food substances have been tested in a small randomized clinical trial for their migraine provoking abilities: red wine, chocolate, and tyramine. Red wine provoked migraine in nine of 11 migraine patients who were preselected on being sensitive for red wine (16). Chocolate triggered migraine in five of 12 'chocolate-sensitive' migraine patients, whereas in a second study the headache response after chocolate did not differ from placebo (17,18). Tyramine (200 mg), a naturally occurring catecholamine analogue-releasing agent found in fermented food, has also been tested in a provocation study in 80 migraine patients and there was no difference in the occurrence of headache between tyramine and placebo (19). This is in agreement with the fact that noradrenaline infusion, under controlled conditions, does not induce headache in healthy subjects (20).

In conclusion, questionnaire studies reported several migraine-provoking food products, but prospective and provocation studies

Table 7.1 Potential triggers for migraine

Weather and other atmospheric variables	Temperature Relative humidity High altitude (hypoxia) Possibly other variables (see Chapter 54)
Nutritional	Alcohol Beer Wine (red and white) Cheese Chocolate Caffeine Ice cream Meat Fish Milk (and other dairy products) Vegetables Citrus fruits Lipids Aspartame Monosodium glutamate Sugar Fasting or skipping meals Fluid deprivation
Stress	Psychological stressors
Hormonal	Female hormones
Lifestyle	Fatigue and sleep Smoking Physical activity Sexual activity
Pharmacological	Nitric oxide donors Calcitonin gene-related peptide Pituitary adenylate cyclase-activating polypeptide Prostaglandins

demonstrated only limited evidence of a causal relation. Many patients report a craving for certain food products prior to the migraine attack, so these factors could be considered premonitory factors instead of trigger factors.

Psychosocial stress

Both acute and chronic exposure to psychosocial stress have been linked to a whole range of diseases, including multiple sclerosis, asthma, and migraine. The current understanding of the relationship between stress and migraine is represented in Figure 7.1. Almost 1000 papers have reported on the relation between stress and migraine (21). The studies differ a lot in terms of design and can roughly be placed in two groups. The first group consists of retrospective and prospective questionnaires looking at stressor load and the perception of the patient. In the second group there are provocation trials and studies looking at the stress response.

Stressor load and patient perception

Many migraine patients consider mental stressors as a strong trigger factor for migraine. In retrospective questionnaire studies, between 31% and 82% of patients reported psychosocial stressors as trigger factor (17,18). These studies only give a global impression regarding the perception of patients and it is difficult to draw clear conclusions. A few studies have addressed the link between the load of potential stressors and migraine prospectively. Three studies looked at the number of life events or job strain and migraine and failed to find a relation (22–24). Prospective studies using diaries looking at the relation between the number of daily hassles and the onset of migraine showed a positive result in two studies (22,25) and a negative result in one (26). Interestingly, in this latter study the number of potential stressors did not change prior to a migraine attack, but the patient perception of the stressors increased. It seems that it is not the number of potential stressors that is changing prior to a migraine attack, but the way patients cope with potential stressors.

Provocations and stress response

There have been few attempts to study the effect of mental stress in migraine under experimental conditions. The cardiovascular

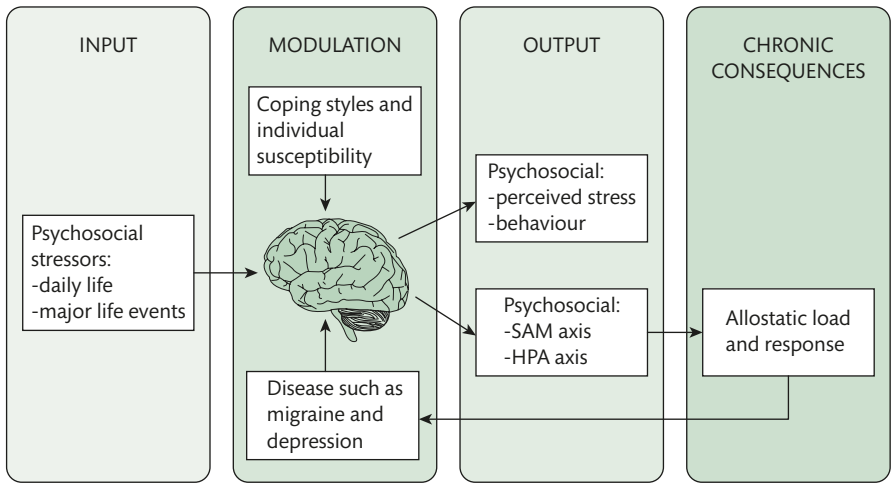

Figure 7.1 Stress cascade and migraine.

Authors' impression of the relationship between stress and migraine. Daily life stressors and major life events are well-known stressors that activate the stress system in humans. The response (both psychological and physiological) is modulated by coping styles and individual susceptibility. Specific disease states such as migraine render the brain more vulnerable to potential stressors. Long-term activation of the physiological stress system results in an increased allostatic load (85) and might, in turn, serve as aggravating factor for migraine.

SAM, sympathetic adrenal medullary axis; HPA, hypothalamic–pituitary adrenal axis.

response to public speaking, low-grade cognitive testing, Stroop test, cold pressor, or a mental arithmetic stressor were not (or only mildly) different between migraine patients and controls (27–29). All of these studies were done interictally. If it were true that coping strategies fail in the hours prior to an attack, it would be of interest to study migraine patients during the onset of an attack.

Female hormones

The menstrual cycle lasts about 28 days and can be divided into the follicular and the luteal phase (see also Chapter 5). The luteal phase starts just after ovulation where the follicle secretes progesterone and oestrogen. If no pregnancy occurs, the corpus luteum persists for 14 days and then degenerates, which leads to a fall in blood oestrogen and progesterone levels, resulting in menstruation.

Changes in female hormones and migraine

The female preponderance in migraine is intriguing and is likely related to female hormones as the male/female (M/F) ratio in migraine changes from childhood (M/F = 1:1) to adults (M/F = 1:3) (30–32). The IHS defines pure menstrual migraine without aura (MO) as attacks occurring exclusively on day 1 ± 2 of menstruation in at least two out of three menstrual cycles and at no other times of the cycle, whereas patients with menstrual-related migraine may also have attacks outside menstruation (3). Two US studies reported that 53–62% of actively cycling patients reported menses as a trigger (33,34). Sixty-seven per cent of women with menstrual-related migraine reported their menstrual migraine to be more severe, more refractory to symptomatic therapy, or of longer duration than their non-menstrual attacks (34). In fact, 25% reported their menstrual migraine to be at least occasionally manifested as status migrainosus (34). Other studies from Europe reported lower incidences of menstruation as a trigger, ranging from 24% to 51% (27,30,31), whereas a study from India reported an incidence of only 13% (35). It appears that menstruation as a trigger appears more frequent in MO (36), and that the resulting attacks are predominately without aura (37). The PAMINA study (38) prospectively analysed data from migraineurs and reported that day 1–3 of menstruation was associated with a hazard ratio of 2.0 for developing migraine attacks in migraineurs. Hormonal alterations during ovulation do not seem to trigger migraine, as shown in two negative studies (39). Oral contraceptives may worsen migraine frequency and intensity in up to 50% of subjects, with no differences between MO and migraine with aura (MA), whereas few improve (40). Furthermore, migraine is more prevalent in postmenopausal women using oral hormone replacement (41). An improvement in migraine is well known during pregnancy, with reports of 80% of women showing complete remission or a higher than 50% decrease in the number of attacks (42). The improvement is most likely during the third trimester (37,38). However, some patients with MA may experience onset or worsening during pregnancy (40).

Potential mechanism

The mechanism behind female hormones as a migraine trigger is likely due to oestrogen withdrawal. Thus, MacGregor et al. (43) prospectively assessed, via daily urine samples, migraine during phases of rising and falling levels of oestrogen across the menstrual cycle (Figure 7.2). The study showed that migraine was significantly more likely to occur in association with falling oestrogen in the late luteal/early follicular phase of the menstrual cycle, and that migraine was significantly less likely during phases of rising oestrogen (43). Withdrawal of oestrogen and progesterone leads to endometrium breakdown and thereby release of prostaglandins into the circulation (37). In support, infusions of prostaglandins induce immediate migraine-like attacks (44,45) and the prostaglandin inhibitor, naproxen, may be effective as short-term prophylaxis in pure menstrual migraine (46).

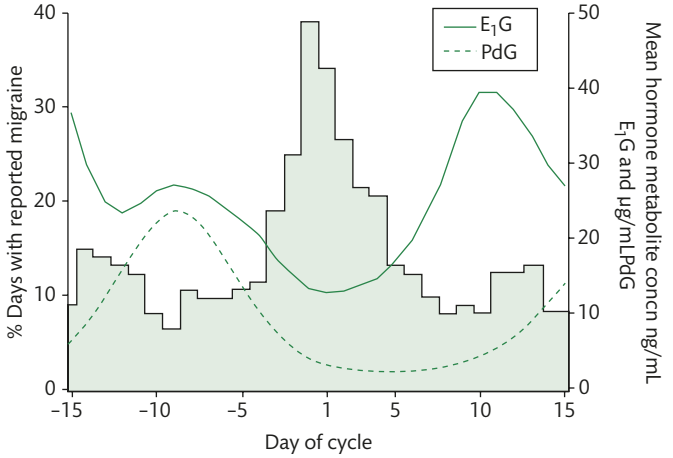

Figure 7.2 Migraine incidence and menstrual cycle.

Incidence of migraine, urinary estrone-3-glucuronide (E_1G) and pregnanediol-3-glucuronide (PdG) levels on each day of the menstrual cycle in 120 cycles from 38 women.

Reproduced from *Neurology*, 67, MacGregor EA, Frith A, Ellis J et al., Incidence of migraine relative to menstural cycle phases of rising and falling estrogen, pp. 2154–2158. Copyright © 2006, American Academy of Neurology. DOI: 10.1212/01.wnl.0000233888.18228.19.

Lifestyle factors

Fatigue and sleep

Sleep has been documented as an important migraine trigger. Fatigue, and sleeping difficulties as a whole, has been reported as a trigger factor by up to 80% of migraine patients versus 56% without migraine (25). Interestingly, both sleep excess and deprivation have been reported as migraine triggers. Thus, studies reported that lack of sleep is a potential migraine trigger in 20–84% of patients (32,47); in contrast, excess sleep has been reported in one study as a trigger by 32% (48). The relationship between sleep and migraine is complex. Migraine is positively associated with a general lack of refreshment after sleep (31), and polysomnographic recordings showed a decrease in cortical activation on nights preceding migraine attacks versus nights without a following attack (49). Furthermore, headache upon awakening has also been reported by 71% of patients in a large clinical sample of migraineurs (17,44), and a prospective study using an electronic diary identified tiredness as a premonitory symptom in 72% of migraineurs (50). The lateral hypothalamus and perifornical area contain hypocretinergic neurons that become active during sleep deprivation (46,51). Such

hypocretinergic neurons may mediate the triggering of a migraine attack when the patient is mildly sleep deprived (52). In conclusion, sleep disturbances are present in many migraine patients and are frequently reported as a migraine trigger. However, it is difficult to differentiate whether sleep disturbances may be a true trigger factor or a premonitory symptom. It is possible that sleep disturbances may be both a trigger factor and an integrative part of the pathophysiology of migraine.

Smoking

Smoke from cigarettes contains many compounds that may be potential migraine triggers. Inhaling smoke also leads to an increase in arterial carbon monoxide, which may induce dilatation of cerebral vessels (53). Smoking has been reported in one retrospective study to be more common in MO than in MA, whereas another study has shown the opposite (48). Whether smoke has a clinical impact was questioned in a prospective study by Chabriat et al. (25), who reported that only 2% of migraineurs experienced smoking as a trigger. Interestingly, a large prospective study showed that smoking increases the risk of aura but decreases the risk of MO, according to multivariate analysis (38). Salhofer-Polanyi et al. (38) hypothesized that avoidance of smoke may be a premonitory symptom characterizing MO patients, but two former studies in a large cohort of patients did not regard changes in smoking habits as a premonitory symptom (45,50). In summary, smoke is a potential trigger in MO and MA, but it is uncertain to what degree. It may also be questioned whether smoke might be a part of premonitory symptoms.

Physical activity

Retrospective studies have reported physical activity as a migraine trigger with a frequency ranging from 13% to 42% (17,54). It is important to differentiate this potential trigger from primary exertional headache, which is defined as a pulsating headache lasting from 5 minutes to 48 hours brought on by and occurring only during or after physical exertion (3). In one prospective study (55) the risk of migraine aura was increased significantly by physical exhaustion on univariate analysis (odds ratio 1.96), but when performing multivariate analysis, taking into account other trigger factors, this trigger was not significantly related to MA (38). Hougaard et al. (56) reported that in MA patients who reported physical activity as a migraine trigger, only one in 12 reported migraine aura after physical activity under controlled conditions in the laboratory. Interestingly, migraine patients have been shown to be significantly more likely to avoid physical activity compared with tension-type headache patients (55), and Wöber et al. (57) also prospectively showed that lack of physical activity increased the risk of headache in migraineurs. In addition, a cross-sectional epidemiological study demonstrated that the level of physical activity showed no association with migraine. Thus, it is likely that physical activity is not in itself a trigger, but avoidance of physical activity may be a premonitory symptom in migraine patients. Furthermore, physical activity may lead to other potential triggers such as stress, heat, and fatigue (17,54).

Sexual activity

There are a few studies reporting sexual activity as potential trigger (see also Chapter 25). The studies have reported relatively low trigger frequencies among migraine patients, ranging from 3% to 5% (17,58). Interestingly, sexual activity may also have a positive effect on migraine headache. Hambach et al. (59) reported in an observational study that 34% of migraine patients had experience with sexual activity during an attack, and out of these patients 60% reported an improvement of their headache. Some patients, in particular male migraine patients, even used sexual activity as a therapeutic tool.

Pharmacological factors

Pharmacological migraine triggers have been systematically examined for many years to study migraine pathophysiology (60). These experiments yield important clues to possible brain structures that may be activated during spontaneous attacks, which may also be used to explain the effect of potential migraine triggers.

Nitric oxide

Nitric oxide (NO) is a well-known migraine trigger. It is a signalling molecule that has many biological functions and has been identified in trigeminal C-fibres (61) and parasympathetic nerve fibres (62) innervating cranial vessels. Food may contain nitrite and nitrate, which are possible exogenous sources of NO. Nitrite and nitrate are food additives (labelled E249–E252) for preserving meat to prevent botulism, and the amounts of nitrite and nitrate in food are controlled by national and European Union authorities to avoid formation of carcinogenic nitrosamines in meat, possibly the reason why there is only a single 1972 case report on 'hot-dog headache' (63). NO may also be delivered via glyceryl trinitrate (GTN), a prodrug used to treat angina and heart failure. Intravenous administration of GTN has been reproducibly shown to induce migraine-like attacks in 80–83% of MO patients (64–66) and 50–67% of MA patients (64,67). Patients typically develop a delayed migraine-like attack, peaking 5 hours after the end of an infusion (66). The exact neurobiological mechanisms of GTN-induced migraine-like attacks have not been fully clarified (62,63). GTN serves as a vasodilator because it is converted to NO in the body. NO is highly lipid soluble and easily penetrates membranes, including the blood–brain barrier. Thus, NO may trigger migraine through peripheral and/or central modulation of the brain. NO also activates intracellular soluble guanylate cyclase and catalyses the formation of cyclic guanosine monophosphate (cGMP). Sildenafil, a selective inhibitor of phosphodiesterase 5, which is the major enzyme responsible for the breakdown of cGMP, has been demonstrated to induce migraine-like attacks in 83% of migraine patients (68), which suggests that migraine might be provoked by upregulation of intracellular cGMP.

Calcitonin gene-related peptide

Trigeminal sensory C-fibres innervating the cranial vessels contain the neuropeptide calcitonin gene-related peptide (CGRP) (69), and electrical stimulation of the trigeminal ganglion liberates vasoactive peptides into the perivascular space (70). The importance of

CGRP in migraine became firmly established when Lassen et al. (71) conducted a double-blind crossover study, where CGRP or placebo was infused for 20 minutes in 12 MO patients. Following CGRP infusion, 67% experienced migraine-like attacks versus only one after placebo. A study by Hansen et al. (72) revealed that CGRP induced MO attacks in 57% of MA patients. Mechanisms responsible for CGRP-induced migraine attacks has not yet been clarified, but CGRP receptor activation leads to increased cyclic adenosine monophosphate (cAMP) levels (73). Cilostazol is an inhibitor of phosphodiesterase 3 that is known to increase intracellular cAMP, and when cilostazol is given to healthy subjects, 92% develop headache, of which 18% have migraine-like features such as pulsating pain quality and aggravation by physical activity (74). These data suggest that the cAMP pathway may play an important role in triggering migraine.

Pituitary adenylate cyclase activating polypeptide

Pituitary adenylate cyclase-activating polypeptide (PACAP) is a signalling molecule found in sensory (75) and parasympathetic nerve ganglia (62) with perivascular nerve fibre projections to intracranial vessels. PACAP38 infusion induced migraine attacks in 58% of MO patients (76). It has been suggested that PACAP38-induced migraine might be caused by selective activation of the PACAP type 1 receptor (77), which, interestingly, shares the same cAMP intracellular signalling pathway as CGRP.

Prostaglandins

Prostaglandins are important mediators of pain and inflammation, and considerable evidence implicates their involvement in the pathogenesis of migraine. Thus, experimental studies have showed that prostaglandin I_2 (PGI_2) (45) and prostaglandin E_2 (PGE_2) (44) induce migraine-like attacks in MO patients. Interestingly, in contrast to delayed NO, CGRP, and PACAP38 migraine attacks, PGI_2 and PGE_2 initiate immediate migraine symptoms during infusion. This suggests that prostaglandins might have modulatory effects in the late course of spontaneous migraine.

Several endogenous signalling molecules found in perivascular intracranial compartments have been identified as migraine triggers. Thus, the described hormonal, nutritional, and physiological triggers may all eventually lead to endogenous release to some of these signalling molecules during spontaneous migraine attack. Drugs targeting blockade of these signalling molecules, before exposure to a certain trigger, may be pursued experimentally to investigate the causative relationship between a trigger and a signalling molecule.

Migraine triggers: many myths and few facts

There is some discrepancy between patient perception of migraine triggering factors (as measured by retrospective questionnaires) and prospective studies. The consistency between retrospective questionnaire studies in various countries is limited. For instance, eating too late or fasting is considered a trigger in 57% of US migraine patients (48) and 1% of Japanese patients (78). Menstruation is a trigger for 65% of US patients and 9% of Chinese patients (79). In a review paper, the prevalence of several non-dietary factors were compared and consistency was also rather low (7). A second example of discrepancy is found in a study concerning Chinook winds. In Canada there is a strong believe that Chinook winds are strong triggers for migraine. In a prospective study, 88% of 34 migraine patients said their migraines were weather sensitive, but an objective correlation could only be confirmed in 21% (80). A third example is chocolate. In retrospective questionnaires around 25% of patients indicated that chocolate is a trigger factor (14). Prospective clinical trials, however, are either negative (17) or show a trend (18).

Potential sources for disagreement between patients' perceptions and prospective studies

Differences in study design

Comparing questionnaire studies with prospective studies is a bit like comparing apples and pears. Questionnaire studies are good for assessing patient perception but that is something different than finding a factual association. The problem with measuring perception is that it can be influenced by, for instance, symptoms generated by the migraine attack. During the onset of a migraine attack patients become sensitive to external stimuli like light and sound, but they can also become sensitive to potential stressors, which, under normal conditions, would not be considered stressful (26).

Variability in migraine susceptibility

The probability of a migraine attack at a certain point in time depends on the severity of the trigger and individual susceptibility. For instance, a female migraine patient might only get a migraine after drinking red wine when she has her menstrual period. In a retrospective questionnaire study she will respond that red wine is a trigger. However, if you do a provocation trial on day 8 of her cycle she will not have an attack.

Clinical implications

Classic advice has been to instruct patients to identify and avoid triggers (4,5). This is despite a very limited amount of research on the effect of coping with migraine triggers by avoidance. Blau and Thavapalan (81) investigated 14 MA and nine MO patients and identified 127 provoking factors. The patients were then instructed to avoid triggers, which led to a 50% reduction in attack frequency within 3 months. However, the patients were also instructed to abort attacks by quickly taking antiemetic and analgesic tablets, which may have been a very important confounder. Martin (82) suggested that migraine patients may, in fact, benefit from exposure to triggers, based on experience from cognitive behavioural therapy in treatment of anxiety and stress. However, whether exposure to a potential trigger may actually be effective as migraine therapy has not yet been investigated.

It is difficult to differentiate between what might be premonitory symptoms or triggering factors in migraine, which seems clear from the reviewed data in this chapter. Hougaard et al. (56) recruited 27 MA patients who reported that bright or flickering light or strenuous exercise triggers their migraine attacks. The patients were experimentally provoked by different types of photo stimulation, strenuous exercise, or a combination of the two. Interestingly, only three patients (11%) reported attacks of MA following provocation. An additional three patients reported MO attacks. Thus, the study shows that experimental provocation using self-reported natural trigger factors causes MA only in a small subgroup of MA patients. In addition, possible migraine triggers may occur at the same time, which makes it difficult for the patient and the treating physician to identify the appropriate trigger. For example, how do we identify and decipher the exact triggering factor if a migraine attack occurs

following jogging for 1 hour, which may induce heat, mild dehydration, and hypoglycaemia, resulting in consumption of a chocolate bar and a feeling of general fatigue? It is also possible that this cascade of possible triggers needs to occur in combination to induce migraine or may depend on the migraine patient's conviction that this may trigger an attack.

Oestrogen withdrawal leading to menstruation-induced migraine is a clear migraine trigger, for which there is evidence that maintaining a stable oestrogen level (83) or prophylactic treatment during oestrogen withdrawal is effective in preventing the attack. Pharmacological triggers such as NO, CGRP, PACAP38, and prostaglandins have also been shown to induce migraine in a controlled experimental setting. Yet, at present, there is no scientific evidence that avoiding or coping with most known migraine trigger factors is effective in migraine treatment. We suggest that patients are advised and informed that some factors may occur prior to a migraine attack but that these factors are not necessarily responsible for the migraine attack. Some of these factors may be symptoms of a developing migraine attack. There is a great demand for future prospective and experimental studies on migraine triggers.

Conclusion

Migraine triggers are identified by many migraine patients and trigger avoidance is recommended as a first step in migraine management. However, prospective studies showed only weak correlations between migraine and weather, food, stress, or lifestyle factors. Only pharmacological triggers like nitroglycerin are able to trigger an attack in more than 75% of patients. There are no convincing clinical trials showing the efficacy of trigger-avoidance strategies as prophylactic treatment for migraine. When instructing a patient it is important to explain the substantial discrepancy between patient perception and objective studies. Many potential triggers can be regarded as premonitory symptoms, but trying to avoid them will not work. For instance, psychosocial stressors are not increased in the 24–48 hours prior to a migraine attack, but the migraine patient is less able to cope with these stressors.

Future studies should focus on both prospective cohort studies and clinical provocation trials. There is no need for new retrospective questionnaires. Before starting a large-scale prospective study on trigger factors, it makes sense to look at the methodology used in genetic studies, such as genome-wide association studies. In fact, environment-wide association studies have revealed new pieces of information for multifactorial diseases like diabetes mellitus type 2 (84) and, hopefully, they will do the same for migraine.

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8

Hemiplegic migraine and other monogenic migraine subtypes and syndromes

Nadine Pelzer, Tobias Freilinger, and Gisela M. Terwindt

Introduction

Migraine with aura (MA) and migraine without aura (MO) both have a strong genetic component. Population-based family studies showed that the familial risk of migraine is increased (1–3). Genome-wide association studies (GWAS) have recently led to the identification of several genetic risk factors for migraine, which confirms that these common forms have a complex genetic background (4–7). To identify pathophysiological mechanisms of a complex genetic disorder it is useful to study monogenic subtypes. Hemiplegic migraine (HM) is such a rare monogenic subtype of MA. Apart from HM, other monogenic syndromes are associated with migraine (**Figure 8.1**). Migraine seems to be part of the clinical spectrum of several monogenic vascular syndromes. Other monogenic syndromes include symptoms that mimic migraine headache or migraine auras, or these syndromes are associated with one of the three known HM genes. Because of these overlapping features, these monogenic syndromes are part of the differential diagnosis when a patient presents with migraine (-like) symptoms. Genetic testing and other diagnostics such as imaging, cerebrospinal fluid (CSF) analysis, or electroencephalography (EEG) may sometimes help to differentiate between these disorders. Making a correct diagnosis is crucial to inform patients not only about the natural history and prognosis of their disease, but also about its heritability and thus the consequences for the patient's relatives. Several genes showed associations with migraine in only a few patients with familial migraine without motor auras (*KCNK18* (8), *CSNK1D* (9)), or in a few patients with HM, often with comorbid disorders (*SLC1A3* (10,11), *SLC4A4* (12)). These genes and disorders are not discussed further in this chapter.

Hemiplegic migraine: a monogenic migraine subtype

HM is a monogenic syndrome in which migraine is the key inherited disorder. HM is considered an official subtype of MA in the International Classification of Headache Disorders (ICHD) (13). HM is rare, with an estimated prevalence of 0.01% (14). Beside common aura symptoms and migraine headaches, attacks include transient hemiparesis varying from mild paresis to hemiplegia. Two types of HM are recognized. In familial HM (FHM) there is at least one first- or second-degree family member with HM attacks. FHM shows autosomal dominant inheritance, which means that any offspring of a patient with HM has a 50% chance of inheriting the genotype. In the third version of the ICHD, FHM is categorized according to the results of genetic testing. FHM1 is associated with mutations in *CACNA1A*, FHM2 with *ATP1A2* mutations, and FHM3 with *SCN1A* mutations (**Figure 8.1**) (see section 'Genetic testing in hemiplegic migraine'). In sporadic HM (SHM), the family history is negative for HM, but migraine often runs in the family (13). Some patients with SHM have de novo mutations and thus a new FHM family may develop if the mutation carrier has offspring in the future (15). The core pathophysiological mechanisms of HM are considered to be similar to those of migraine, especially MA, and patients with HM report similar trigger factors as patients with common subtypes of migraine (16), although experimental studies also showed different triggering effects in HM (17–20).

Clinical symptomatology of hemiplegic migraine

Clinical diagnosis of HM is based on the ICHD criteria of the International Headache Society (**Box 8.1**), which makes the physician's interview the most important step of the diagnostic process (13). A physical examination is mainly performed to exclude other disorders. To distinguish familial HM from sporadic HM, obtaining the family history is essential.

Compared with the general population, patients with HM have an increased risk of also suffering attacks of the common forms of migraine with and without aura, with a co-prevalence risk of 55% for MA and 25% for MO (21). Because of this co-occurrence of several migraine subtypes in one patient, it may be difficult for patients to discern which symptoms occur during which type of attacks, and the interview can therefore be complicated.

To conclude whether a patient suffers from HM, a motor aura must be present. When patients experience complete hemiplegia, they often report these symptoms spontaneously, but a mild paresis that is, for example, limited to one extremity may be difficult

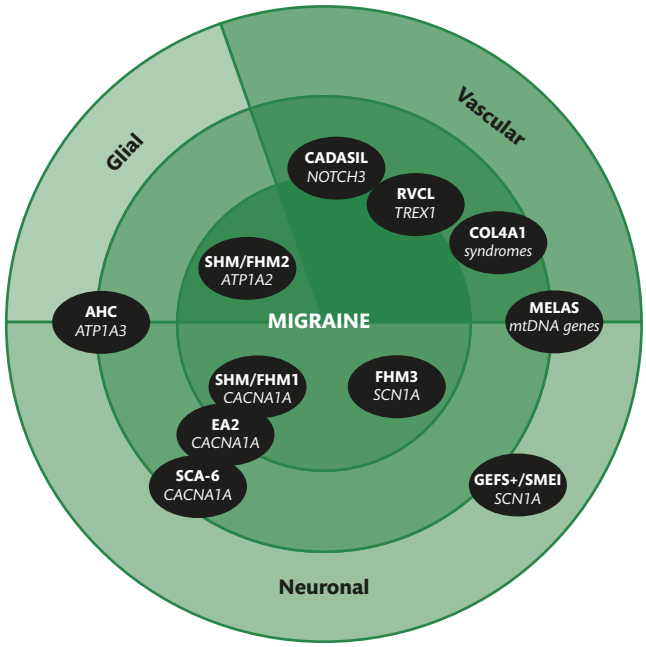

Figure 8.1 Monogenic syndromes associated with migraine (and their causative genes).

CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; RVCL-S, retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations; MELAS, mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke (associated with mutations in mitochondrial DNA (mtDNA); GEFS+/SMEI, generalized epilepsy with febrile seizures/severe myoclonic epilepsy of infancy; SCA-6, spinocerebellar ataxia type 6; EA2, episodic ataxia type 2; SHM/FHM, sporadic hemiplegic migraine/familial hemiplegic migraine; AHC, alternating hemiplegia of childhood.

to establish retrospectively. The biggest difficulty is to distinguish complaints of sensory disturbances from those of a mild paresis, because sensory auras may cause the sensation of being unable to grasp or lift objects and might be interpreted as mild motor auras. This diagnostic problem also arises when patients are asked whether relatives with migraine suffer from motor weakness during attacks. To diagnose FHM it is therefore always necessary to obtain a direct interview from all family members to verify whether multiple relatives do indeed suffer from motor auras, and not common MA.

Apart from the HM-specific motor auras, the symptoms and their order of appearance during attacks are very similar for HM and MA (22). Possible clues towards HM are the occurrence of two or more aura subtypes (e.g. visual, sensory, and motor auras), aura symptoms of longer duration, and brainstem auras (i.e. dysarthria, vertigo, tinnitus, hypacusis, diplopia, ataxia, and/or decreased level of consciousness) (13,22,23). In addition, the attack frequency of HM is variable, but with an average of three attacks per year it is much lower than that of MA and MO (24). The mean age at onset of FHM is lower than the average in common migraine subtypes. In familial MA, a mean age at onset of 21 years has been reported versus 17 years (95% confidence interval 15–18; range 1–45 years) or even 11.7 years (standard deviation 8.1, range 1–51) in FHM (22,25). Similar to common migraine subtypes, HM is 2–4 times more prevalent in females (14,22). A typical HM feature is triggering of attacks by a minor head trauma, with an average prevalence of 9% in a large FHM cohort (25).

Severe HM attacks may be prolonged (up to 6 weeks) and accompanied by confusion, decreased consciousness, fever, seizures, and even coma (25–27). These severe symptoms and also the typical HM symptoms may divert physicians to other diagnoses, resulting in a need for additional diagnostics.

Box 8.1 Criteria for hemiplegic migraine

1.2.3 Hemiplegic migraine

Description:

Migraine with aura including motor weakness.

Diagnostic criteria

A Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below.

B Aura consisting of both of the following:

C fully reversible motor weakness;

D fully reversible visual, sensory and/or speech/language symptoms.

Notes:

1 The term *plegic* means paralysis in most languages, but most attacks are characterized by motor weakness.

2 Motor symptoms generally last less than 72 hours but, in some patients, motor weakness may persist for weeks.

Comment:

It may be difficult to distinguish weakness from sensory loss.

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Role of additional diagnostics and differential diagnosis of hemiplegic migraine

Imaging and vascular events or structural abnormalities

Especially in the acute phase of a first HM attack, a transient ischaemic attack (TIA) or stroke is often part of the differential diagnosis. A discerning factor is that migraine auras often start gradually, with a series of consecutive and spreading symptoms, in contrast to the sudden onset of vascular events.

Genetic testing can solve the diagnostic problem, but it may take up to several months before the results are available. In the meantime, it is important to consider other diagnoses. When HM attacks always occur on the same side, underlying pathologies, including arteriovenous malformations, arterial dissections, and cerebral vasculitis, must be excluded by magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA). There are only a few permanent imaging abnormalities (i.e. abnormalities that are also present in the interictal phase) that can support the diagnosis of HM. In patients with FHM type 1 (FHM1) patients with progressive cerebellar ataxia, cerebellar atrophy has been described (Figure 8.2) (28,29). In a few cases, diffuse cortical and subcortical hyperintensities on T2-weighted MRI (30–32), signs of ischaemic necrosis (33), or cortical cerebral atrophy (30–32,34) were still visible in the previously affected hemisphere.

The majority of radiological abnormalities in HM have been found during or shortly after a HM attack. Even during an attack, however, it is difficult to determine whether the observed abnormalities are primary or secondary. The ictal computed tomography (CT) or MRI abnormalities are reversible and may be linked to both vascular and neuronal mechanisms. Diffuse (cortical) oedema of the hemisphere contralateral to the motor deficit is the most prevalent observation (Figures 8.2 and 8.3) (31,35–37). The oedema may be

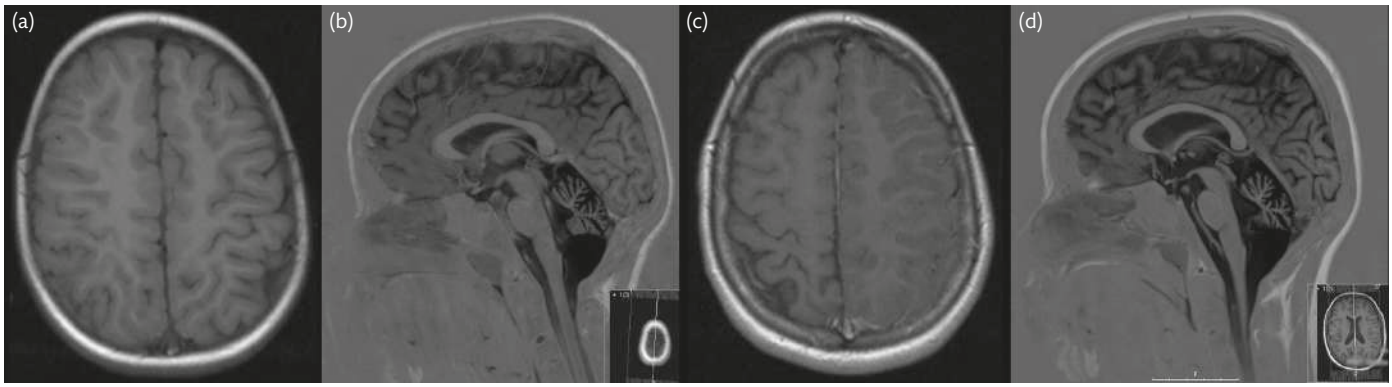

Figure 8.2 Consecutive magnetic resonance imaging (MRI) scans over a 10-year follow-up period in familial hemiplegic migraine.

The patient carries the p.Ser218Leu *CACNA1A* mutation and suffers from psychomotor retardation and progressive cerebellar ataxia. (A, C) Axial T1-weighted MRIs during ictal phases showing diffuse cortical swelling of both the (A) right and (C) left hemisphere during separate hemiparetic attacks with a 9-year interval. (B, D) Sagittal T1-weighted inversion recovery MRI showing progressive cerebral and cerebellar atrophy with a 2-year interval.

cytotoxic, as is suggested by MRIs that show reversible decrease in water diffusion (35,38). Mild gadolinium enhancement on MRI has also been reported, which indicates opening of the blood–brain barrier and thus points towards vasogenic oedema (38–40). Reported abnormalities in cerebral perfusion during a HM attack are diverse and definite conclusions cannot be made (31,40,41).

Both conventional angiography and MRA have shown narrowing or even obliteration of intracranial arteries during a HM attack, but subsequent signs of ischaemia were not observed (42,43). In contrast, a case report demonstrated dilatation of the middle cerebral artery (40). Conventional cerebral angiography via a catheter is contraindicated in HM, because it has been reported to provoke HM attacks, or worsen a patient's condition dramatically (25,27,32,44). Modern alternatives such as MRA or CT angiography are therefore recommended.

Electroencephalography and epilepsy

Epilepsy and HM often co-occur, mainly in FHM type 2 (FHM2) and FHM type 3 (FHM3). Patients may suffer from migraine and epileptic features during the same episode, or experience separate migraine attacks and epileptic seizures. It may be difficult to determine whether visual symptoms are auras or epileptic phenomena, and Todd's palsies may be confused with motor auras (25,45,46). Epilepsy symptoms can be distinguished by their more sudden onset than migrainous symptoms.

EEGs during and after HM attacks have shown diffuse one-sided slow waves (theta and/or delta activity) in the hemisphere contralateral to the side of the motor symptoms (47). Epileptic features such as spike-and-wave complexes have only been found in cases with simultaneous HM attacks and epileptic seizures (29,45).

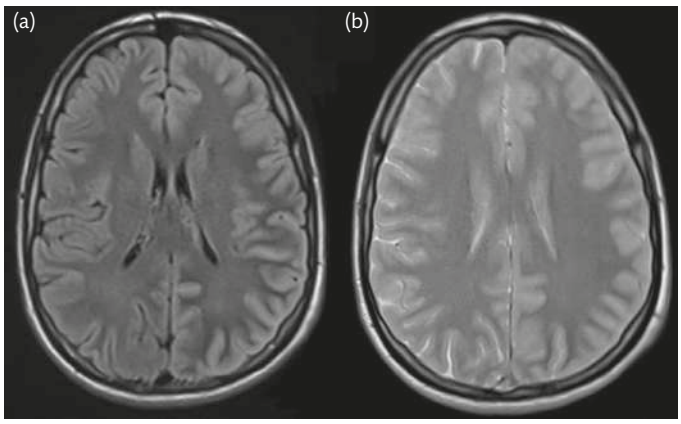

Figure 8.3 Magnetic resonance imaging (MRI) during the ictal phase of a hemiplegic migraine attack.

Patient with right-sided hemiparesis, aphasia, and migraine headache. (A) T2-weighted and (B) fluid-attenuated inversion recovery T2-weighted MRI showing generalized cortical swelling of the left hemisphere.

Cerebrospinal fluid analysis and meningo-encephalitis or transient headache with neurological deficits and CSF lymphocytosis

Patients with HM may present with confusion, altered consciousness, and fever during an attack, which warrants a lumbar puncture to exclude an infectious aetiology. Lumbar punctures performed during HM attacks have revealed CSF lymphocytosis of up to 350 cells per mm^3 and elevated protein levels of up to 228 mg/dl in patients who occasionally had fever but no meningeal signs (28,48–51). CSF cultures and virological tests subsequently turned out negative. This phenomenon is probably a meningeal reaction secondary to a migraine attack or, less likely, the migraine may be secondary to an aseptic meningitis. To establish the diagnosis, it is important to note that increased CSF cell counts and protein levels may occur during HM attacks.

The condition of transient headache with neurological deficits and CSF lymphocytosis (HaNDL) shows a remarkable resemblance to HM (see also Chapter 44) (52,53). Approximately 100 cases have been described with CSF lymphocytosis, often with increased protein levels, and normal neuroimaging, CSF culture, and virological tests. Additional characteristics, such as transient, focal, non-epileptiform EEG changes, provocation of attacks by cerebral angiography, and even reversible radiological abnormalities, are also reported (52–55). Visual auras are a very common feature in HM (89–91% of patients), but were only reported by 18% of patients with HaNDL (24,52). Approximately half of patients with HaNDL describe a viral prodrome and fever, which is not as common in cases of HM, although an incidental fever has been described. The only HaNDL criterion that truly conflicts with HM is that HaNDL, by

definition, has to resolve spontaneously within 3 months. Although the duration of follow-up in some patients with HaNDL was up to 3 years, it remains difficult to determine whether the symptoms really did not recur. Because of the many overlapping features between HM and HaNDL, it may be considered that HaNDL is part of the HM phenotypic spectrum. One study evaluated this hypothesis by screening the *CACNA1A* gene in patients with HaNDL, but no mutations were found. However, this study only included eight patients, and the other HM genes have not yet been tested in patients with HaNDL (56).

Genetic testing in hemiplegic migraine

So far, three genes have been associated with HM, indicating that HM is genetically heterogeneous (**Box 8.2**). *PRRT2* (also associated with benign familial infantile seizures, paroxysmal kinesigenic dyskinesia, and infantile convulsion choreoathetosis syndrome (57)) has been suggested as the fourth HM gene, but further evidence is needed to support this claim (58). Based on clinical symptoms during HM attacks alone, subtypes of HM cannot be distinguished, but the presence of additional symptoms (such as chronic progressive ataxia or epilepsy) may be suggestive of certain genetic subtypes. FHM1 and SHM type 1 are caused by mutations in *CACNA1A* on chromosome 19p13, encoding the ion-conducting α_{1A} -subunit of P/Q-type voltage-gated Ca^{2+} channels (59). These channels are localized in dendrites and presynaptic nerve terminals of central neurons and trigger neurotransmitter release (60). Over 25 *CACNA1A* missense mutations, leading to a gain of function of the Ca^{2+} channels, have been associated with FHM1 (60). Apart from the pure HM symptoms described in the ICHD criteria, the clinical spectrum of reported FHM1 families includes chronic progressive cerebellar signs, permanent cognitive deficits, and decreased level of consciousness and seizures during HM attacks (25,28,61). The p.Ser218Leu *CACNA1A* mutation is associated with a very severe phenotype of seizures triggered by minor head trauma, followed by cerebral oedema and even fatal coma (26).

The second HM gene, *ATP1A2* on chromosome 1q23, encodes the α_2-subunit of Na^+/K^+-ATPase. This pump creates a steep sodium gradient by exchanging Na^+ ions for K^+ ions, thereby facilitating the removal of K^+ and glutamate from the synaptic cleft into glial cells (60). The majority of the total number of HM mutations has been identified in *ATP1A2*, with nearly 50 unique *ATP1A2* mutations, mostly missense mutations, reported so far. The mutations appear to result in a loss of function of the Na^+/K^+-ATPase (60,62). Additional paroxysmal neurological symptoms have been described in patients with FHM2, including epilepsy, confusion, decreased consciousness, or even coma and prolonged hemiplegia, and also permanent neurological symptoms such as mental retardation (27,46,47,60,63). Progressive cerebellar signs that have frequently been reported with *CACNA1A* mutations are rarely seen in patients with *ATP1A2* mutations (64).

In a few families, missense mutations in a third gene have been detected. *SCN1A* on chromosome 2q24 encodes the α-subunit of voltage-gated Na^+ channels (65). It has been suggested that the voltage-gated Na^+ channels are primarily expressed on inhibitory central neurons (66). When these channels are dysfunctional, as suggested by experiments in heterologous expression systems, this is predicted to lead to neuronal hyperexcitability and FHM attacks (65,67). Of note, *SCN1A* is an important epilepsy gene, with hundreds of mutations identified in monogenic epilepsy syndromes, including Dravet syndrome (also known as severe myoclonic epilepsy of infancy (SMEI)) and generalized epilepsy with febrile seizures plus (GEFS+). The functional effects associated with epilepsy mutations are usually more pronounced than in FHM3; however, the pathophysiological basis of mutations in the same gene leading to migraine versus epilepsy still remains incompletely understood (68). As *SCN1A* mutations were not identified in large groups of SHM patients, it can be justified to refrain from systematic screening of *SCN1A* in SHM (69,70).

The main pathophysiological mechanism thought to underlie HM is that all mutations lead to increased cerebral levels of K^+ and glutamate in the synaptic cleft, which would increase neuronal excitability, and thereby can explain the increased susceptibility to cortical spreading depression (CSD) (**Figure 8.4**) (60).

When a patient exhibits a typical HM phenotype, it is difficult to predict whether a mutation in one of the HM genes will be detected. In large FHM cohorts *CACNA1A* mutations were detected in 4–7% (71,72) and *ATP1A2* mutations in 7% (71). Mutation detection rates in SHM vary even more, with *CACNA1A* mutations in 1–36% (69,70,73,74) and *ATP1A2* mutations in 1–56% (69,70,73). A likely cause for the reported low detection rates is that severe migraine with aura may be confused with HM. Detection rates in SHM appeared to be higher in early-onset SHM, especially when associated with additional neurological symptoms, which confirms that an early age at onset is a feature that may distinguish HM from migraine with aura (69). It appears that not all individuals carrying an HM mutation develop the HM phenotype, as unaffected relatives of patients with HM also carried *CACNA1A* or *ATP1A2* mutations (63,70,71). This reduced penetrance has not yet been reported in

Box 8.2 Criteria for the subtypes of hemiplegic migraine based on genetic testing and family history

1.2.3.1 Familial hemiplegic migraine (FHM)

A Attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine* (see Box 8.1).

B At least one first- or second-degree relative has had attacks fulfilling criteria for 1.2.3 *hemiplegic migraine*.

1.2.3.1.1 Familial hemiplegic migraine 1 (FHM1)

A Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*.

B A mutation in the *CACNA1A* gene has been demonstrated.

1.2.3.1.2 Familial hemiplegic migraine 2 (FHM2)

A Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*.

B A mutation in the *ATP1A2* gene has been demonstrated.

1.2.3.1.3 Familial hemiplegic migraine 3 (FHM3)

A Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*.

B A mutation in the *SCN1A* gene has been demonstrated.

1.2.3.1.4 Familial hemiplegic migraine (FHM) other loci

A Attacks fulfilling criteria for 1.2.3.1 *Familial hemiplegic migraine*.

B Genetic testing has demonstrated no mutation in the *CACNA1A*, *ATP1A2*, or *SCN1A* genes.

1.2.3.2 Sporadic hemiplegic migraine

A Attacks fulfilling criteria for 1.2.3 *Hemiplegic migraine*.

B No first- or second-degree relative fulfils criteria for 1.2.3 *Hemiplegic migraine*.

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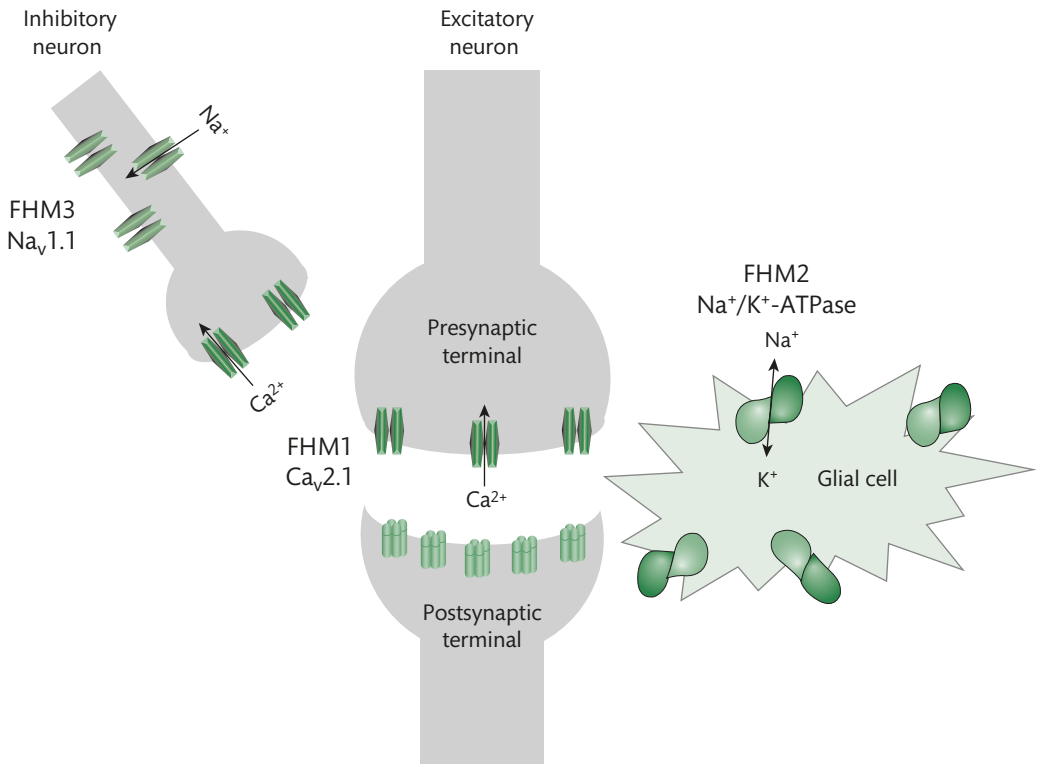

Figure 8.4 Schematic representation of a glutamatergic synapse and the functional roles of proteins encoded by the familial hemiplegic migraine types 1, 2, and 3 (FHM1, FHM2, and FHM3) genes.

In response to an action potential, calcium enters the presynaptic terminal of excitatory neurons via voltage-gated calcium channels ($Ca_v2.1$), encoded by *CACNA1A*. As a result, glutamate will be released into the synaptic cleft. Glial cells (astrocytes) contain Na^+/K^+-ATPase, which is encoded by *ATP1A2* and aids in removing potassium from the synaptic cleft. The removal of extracellular potassium creates a Na^+ gradient, which leads to the uptake of glutamate by other transporters. The voltage-gated sodium channels ($Na_v1.1$) encoded by *SCN1A* play a major role in the generation and propagation of action potentials. FHM1 mutations cause a gain-of-function effect, and FHM2 and FHM3 mutations likely have loss-of-function effects. All FHM mutations appear to result in increased cerebral levels of K^+ and glutamate in the synaptic cleft, and thereby cause an increased excitability, which may explain the increased susceptibility to cortical spreading depression, which is thought to be the underlying mechanism of the migraine aura.

FHM3, although only five clear FHM-associated *SCN1A* mutations have been described so far (60).

It is likely that more HM genes remain to be identified, as some clinically affected individuals do not have a mutation in any of the known genes. Negative test results for mutations in *CACNA1A*, *ATP1A2*, and *SCN1A* therefore do not exclude the clinical diagnosis of HM. Over the past years, GWAS have been successful in identifying susceptibility loci for the common forms of migraine, but HM is too rare to perform such studies (4–7). New analytic techniques such as next-generation sequencing may enable the identification of novel HM genes in the near future (75,76). The importance of taking comorbid disorders into account is illustrated by the finding that mutations in CSNK1D, associated with familial advanced sleep phase syndrome, may also contribute to the pathogenesis of migraine (9).

Treatment of hemiplegic migraine

Before considering medication to treat HM, some lifestyle advice can be discussed. Various trigger factors, such as stress, sleep disturbances, physical exertion, bright lights, drinks, and food products, have all been reported in HM (16). However, especially stress, but possibly other trigger factors as well, is suggested to be part of the premonitory phase of the migraine attack, rather than a true trigger factor (77). This does not apply to the triggering of attacks by (minor) head trauma, which is often and convincingly described in HM. The head trauma-triggered attacks are often reported to be severe, sometimes including coma, or even fatal in specific cases with the p.S218L *CACNA1A* mutation (25,26,28,41,45,47). Because of these reports, patients with HM must be advised not to practice contact sports, or, for example, avoid heading balls when playing soccer. No evidence-based advice can be given about other lifestyle or dietary factors.

Because of the rarity of HM, large clinical drug trials have not been performed and treatment largely follows guidelines for the common forms of migraine. Preference for certain drugs is mostly based on empirical data and the personal experience of the treating neurologist. There are no specific treatments for patients with known mutations. Although the aura symptoms in HM are often more debilitating than the headache, most migraine-specific drugs for acute treatment unfortunately only affect headache.

The first choice in acute treatment is usually acetaminophen or a non-steroidal anti-inflammatory drug. When these do not relieve headaches sufficiently, triptans can be prescribed. The use of triptans was previously controversial because of a fear of migrainous strokes or aggravation of auras, but as CSD is now thought to underlie auras, this contraindication does not apply anymore. Several studies in

patients with HM showed that side effects of triptans were rare and minor (78,79).

The evidence for alternative options in acute treatment of HM is limited. A few case reports suggested the possible efficacy of abortive treatment with intravenous verapamil and acetazolamide in HM (80–83). Other studies have reported some beneficial effects of acute treatment with ketamine nasal spray in HM (84,85). Although these results appear promising, these drugs are not yet considered suitable for widespread use in HM (86).

Prophylactic treatment is often prescribed to reduce high attack frequencies, and may also be considered with low-frequent but severe attacks. Lamotrigine, flunarizine, sodium valproate, verapamil, and acetazolamide can be tried, in no strictly preferred order (86). Other migraine prophylactics, such as topiramate, candesartan, and pizotifen can also be considered, although there is less evidence for the efficacy of these drugs. Reports of adverse effects in HM makes propranolol more controversial, but the evidence of these effects is insufficient to contraindicate beta blockers (see **Box 8.3**) (86).

Box 8.3 Recommendations for clinical practice when suspecting hemiplegic migraine (HM) in a patient

Patient interview

- Confirm the presence of motor aura symptoms and distinguish these from sensory aura symptoms.
- Identify additional features during attacks that point towards HM:
  - epilepsy;
  - confusion;
  - fever;
  - decreased consciousness;
  - other symptoms of brainstem auras;
  - prolonged aura symptoms.
- Identify additional features outside attacks that point towards HM:
  - epilepsy;
  - ataxia.
- Obtain family history:
  - direct interview with first- and/or second-degree relatives to investigate familial occurrence of HM;
  - take into account the possibility of reduced penetrance in relatives (63,70,71).

Additional diagnostics

- Molecular genetic testing:
  - mutations in *CACNA1A*, *ATP1A2*, or *SCN1A*.
- MRI:
  - progressive cerebellar (and cerebral) atrophy;
  - diffuse (cortical) oedema of the hemisphere contralateral to the motor deficit during attacks.
- Cerebrospinal fluid analysis:
  - pleocytosis during attacks.
- Electroencephalography:
  - diffuse one-sided slow waves (theta and/or delta activity) in the hemisphere contralateral to the motor deficit during attacks.

Treatment

- Acute treatment (86):
  - conform treatment of common migraine types, including triptans.
- Prophylactic treatment (in no strictly preferred order) (86):
  - lamotrigine, flunarizine, sodium valproate, verapamil, and acetazolamide.

Vascular monogenic syndromes associated with migraine

Some monogenic syndromes show a higher prevalence of migraine than would be expected based on the population risks. Other symptoms of these disorders are primarily vascular, and unravelling pathophysiological mechanisms of these disorders may reveal vascular mechanisms that also play a role in migraine pathophysiology. The following syndromes should be considered when a family history not only includes many migraine patients, but also many relatives with (early-onset) (cerebro)vascular disease and dementia. Radiological imaging is often helpful in the diagnostic process of these syndromes.

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy

Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) is the most common familial small-vessel disease, with an estimated prevalence of approximately two per 100,000 adults (87). The disease has previously been described as hereditary multi-infarct dementia, chronic familial vascular encephalopathy and familial subcortical dementia, but after the discovery of mutations in *NOTCH3* in 1993 has primarily been referred to as CADASIL (88,89).

Clinical symptomatology of CADASIL

CADASIL is a systemic vascular disease, with varying clinical presentation, even among relatives with the same mutation. Approximately 20–40% of patients suffer from migraine, predominantly MA (90). In half of these cases, attacks are atypical with prolonged, brainstem or hemiplegic auras (or even confusion), fever, meningeal signs, or coma (91,92). During gestation and shortly after childbirth there appears to be an increased risk of transient neurological symptoms, which are later often labelled as migraine auras (93). In these women, and also in other cases, migraine is often the presenting symptom, with a mean age at onset of 26 years (90,94). Mood disturbances occur in 20% of cases, including severe depressive episodes. Apathy is observed in about 40% of patients with CADASIL, which may be accompanied by depressive symptoms, but also occurs without depression (89). A key symptom that should raise the suspicion of CADASIL is the occurrence of TIAs and ischaemic stroke before the age of 50 years (mean age at first event is 48 years, range 19–67 years) (95). After recurrent (lacunar) strokes and cerebral microangiopathy, patients often develop progressive cognitive disturbances, which have also been observed as an isolated finding in 10% of patients (89). About three-quarters of patients eventually develop (vascular) dementia (95).

In patients presenting with MA, especially with the aforementioned atypical features, it is thus important to obtain a thorough family history of cerebrovascular events and early-onset dementia. If a pattern of autosomal-dominant inheritance can be derived, this further points towards CADASIL. However, the disease can also result from a de novo mutation, in which case the family history is negative (96).

Treatment options for CADASIL are limited and non-specific. Migraine attacks can be treated according to common guidelines. In contrast to what is often thought by clinicians, acute antimigraine

medication, such as triptans, can be safely prescribed. Other co-occurring disorders, such as hypertension, hypercholesterolaemia, and diabetes, should also be treated symptomatically. As in other cerebrovascular diseases, patients should be advised to refrain from smoking, as smoking increases the risk of stroke, also for CADASIL specifically (97). Antiplatelet treatment may be used, but its efficacy is not proven in CADASIL. Anticoagulants may provoke cerebrovascular accidents and are therefore contraindicated. Conventional angiography is contraindicated for the same reasons (98). Intravenous thrombolysis is thought to increase the risk for cerebral haemorrhage, which should be conveyed to the treating physicians in the acute phase of a CADASIL-related stroke.

A study of over 400 patients with CADASIL revealed a reduced life expectancy, especially in men. The median age at death was 68 years. The most frequent cause of death was pneumonia; other causes were sudden unexpected death and asphyxia. Most patients were completely dependent or even confined to bed during the final stage of the disease (95). Although there is some therapeutic advice to be given, CADASIL is an incurable and fatal disease. When there is a clear clinical suspicion of CADASIL, (genetic) counselling in a specialized centre is therefore strongly advised before any diagnostics (MRI, skin biopsy, or genetic screening) are performed.

Imaging in CADASIL

The suspicion of CADASIL often arises when MRI reveals symmetrically distributed MRI white matter hyperintensities in the periventricular and deep white matter. T2 signal abnormalities in the white matter of the temporal pole and in the external capsule have frequently been described (Figure 8.5). These hyperintensities may be subtle, but are consistently seen from 21 years of age onwards. Distinctive white matter lesions often first appear in the anterior temporal lobes, while the remaining white matter appears unaffected (99). The load of white matter hyperintense lesions increases during the course of the disease, to a state where all white matter appears to be affected (100). Additional radiological findings include subcortical lacunar lesions at the junction of the grey and white matter in approximately two-thirds of patients and cerebral microbleeds, which mainly occur in the thalamus (98,101,102). Haemodynamic imaging studies reported decreased total cerebral blood flow and decreased cerebral perfusion in normal and abnormal appearing white matter (103,104). Also, areas of white matter lesions exhibited decreased vasoreactivity, which would be consistent with the expected degeneration of vascular smooth muscle cells (vSMCs) (105). Cerebrovascular reactivity measurements after acetazolamide administration in patients with CADASIL were of prognostic value regarding cerebrovascular pathologies (106).

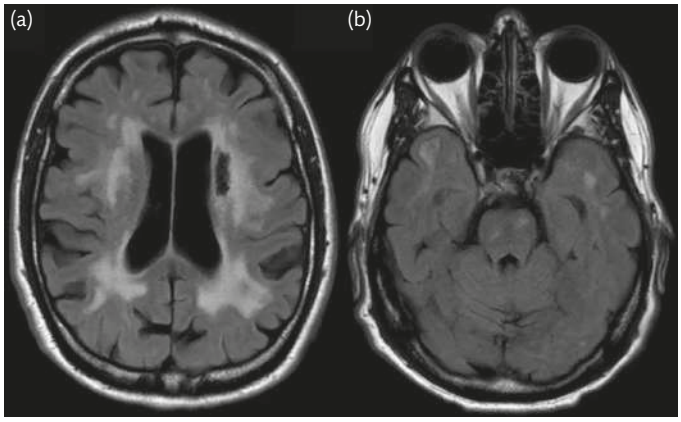

Figure 8.5 Magnetic resonance imaging abnormalities in a patient with CADASIL.

Axial T2-weighted fluid-attenuated inversion recovery images showing extensive symmetric white matter abnormalities in (A) the periventricular areas and in (B) the temporal poles.

Pathophysiology of CADASIL

NOTCH3 is predominantly expressed in vSMCs, preferentially in small arteries. *NOTCH3* encodes a single-pass transmembrane receptor, composed of an intra- and extracellular domain. Most identified *NOTCH3* mutations lead to a loss or gain of a cysteine residue in one of the epidermal growth factor repeats of NOTCH3 (107). The mutations are thought to affect folding of the protein by disrupting disulphide bonding of the cysteine residues. Other hypotheses suggest the receptor cannot be internalized properly, which could result in enhanced ligand binding or toxic effects (108). The majority of *NOTCH3* mutations are clustered in exons 2–6 (109). Microscopic and ultrastructural investigations show a specific arteriopathy affecting mainly the small cerebral and leptomeningeal arteries, characterized by a thickening of the arterial wall leading to lumen stenosis, a largely normal endothelium, the appearance of pathognomonic granular osmiophilic deposits, termed granular osmiophilic material (GOM) within the media extending into the adventitia, and degeneration of vSMCs. The GOM is extracellular, located close to the cell surface of vSMCs, but it can occasionally be found in capillaries. The presence of GOM is highly specific for CADASIL and can be confirmed with electron microscopy of small vessels obtained via a skin biopsy, which may serve as an alternative diagnostic method besides screening of *NOTCH3*. It should be noted, however, that the deposition can be focal and could be missed if the specimen is not thoroughly evaluated (110). Exclusion of the diagnosis based only on a negative skin biopsy is therefore not recommended. DNA analysis is the gold standard.

Although the same morphological changes have been established repeatedly, the pathophysiological mechanisms that eventually cause the CADASIL phenotype remain elusive. Mutations in *NOTCH3* in patients with CADASIL may lead to dysfunction of the blood–brain barrier due to degeneration and loss of pericytes (111,112). A remarkable finding that illustrates the unanswered questions in CADASIL pathophysiology is the fact that clinical manifestations are only cerebral, although arteriopathy is also present in other organs, such as the spleen, liver, kidneys, muscle, aorta, and skin (90,113).

Retinal vasculopathy with cerebral leukoencephalopathy and systemic manifestations

A collection of hereditary neurovascular syndromes with retinal involvement and other systemic symptoms all appeared to be associated with mutations in *TREX1*. After this discovery in 2007, these syndromes (cerebroretinal vasculopathy; hereditary vascular retinopathy; and hereditary endotheliopathy with retinopathy, nephropathy, and stroke) were designated as retinal vasculopathy with cerebral leukodystrophy (RVCL) (114). Heterozygous mutations in *TREX1* have been found in 11 families from Europe, North America, Asia, and Australia (115–121). Although RVCL currently appears

to be very rare—the gene was discovered only a few years ago—the condition is therefore likely still underdiagnosed. The acronym 'RVCL' has recently been replaced by 'RVCL-S' (for 'RVCL and systemic manifestations') (122).

Clinical symptomatology of RVCL-S

RVCL-S is primarily characterized by progressive loss of vision due to a retinal vasculopathy. In addition, a wide range of cerebral and systemic conditions, including intracerebral mass lesions and white matter lesions with associated focal neurological symptoms and cognitive impairment, migraine (primarily without aura), Raynaud's phenomenon, anaemia, and liver and kidney dysfunction can be detected (118). Especially in a large Dutch RVCL-S family, MA and Raynaud's phenomenon—an abnormal vasomotor reaction in response to cold exposure—are prominent in the phenotype (123). A genetic association study demonstrated an increased susceptibility for both Raynaud's phenomenon and migraine for the RVCL-S haplotype (124). A treatment to cure RVCL-S is not available, but some symptomatic treatment can be tried. The common policy for migraine treatment can be followed, and the retinopathy can be halted by laser therapy. The anaemia, liver, and kidney dysfunction often do not appear to require treatment, but it remains unclear if this applies to all patients with RVCL-S. The consecutive disease stages of RVCL-S, especially the early stages, remain to be identified. Life expectancy in RVCL-S patients is decreased, with an average age at death of 53.1 years (range 32–72 years). In most described cases the cause of death was a pneumonia or sepsis in the setting of general debilitation (122).

Imaging in RVCL-S

When a patient presents with symptoms suggestive of RVCL-S, radiological imaging can strengthen this suspicion, or other syndromes, such as CADASIL, may become a more likely diagnosis. All abnormalities on CT and MRI that have so far been described in patients with RVCL-S are restricted to the white matter. The lesions are non-specific but remarkable for the patients' relatively young age. Two types of lesions have been observed: (i) focal, non-enhancing T2-hyperintense lesions scattered throughout the periventricular and deep white matter; (ii) hyperintense mass lesions on T2 and hypointense lesion on T1-weighted images, enhanced with gadolinium contrast, and often surrounded by extensive oedema, displacing adjacent structures and leading to sulci effacement (**Figure 8.6**) (117,118). These mass lesions are often referred to as 'pseudo-tumours' (119,125). Mass lesions have been reported in 75% of patients with RVCL-S, most often in later stages of the disease. Lesions are localized in the frontoparietal lobe in all patients, sometimes with additional lesions in the cerebellum and occipital lobe. These lesions have been observed to increase in size, remain stable, or diminish in size. Restricted diffusion has occasionally been observed, mainly in the centre of these lesions, but it remains unclear whether this reflects local ischaemic changes or demyelination. In approximately half of patients, mass lesions are associated with calcifications on CT. In some cases, mass lesions develop superimposed on pre-existing aspecific non-enhancing white matter hyperintensities, sometimes associated with pre-existing or developing calcifications. Haemorrhage is reported only very rarely (122). Imaging in presymptomatic *TREX1* mutation carriers has not been performed systematically, and it is unclear whether mild intracerebral lesions may already be present in these individuals.

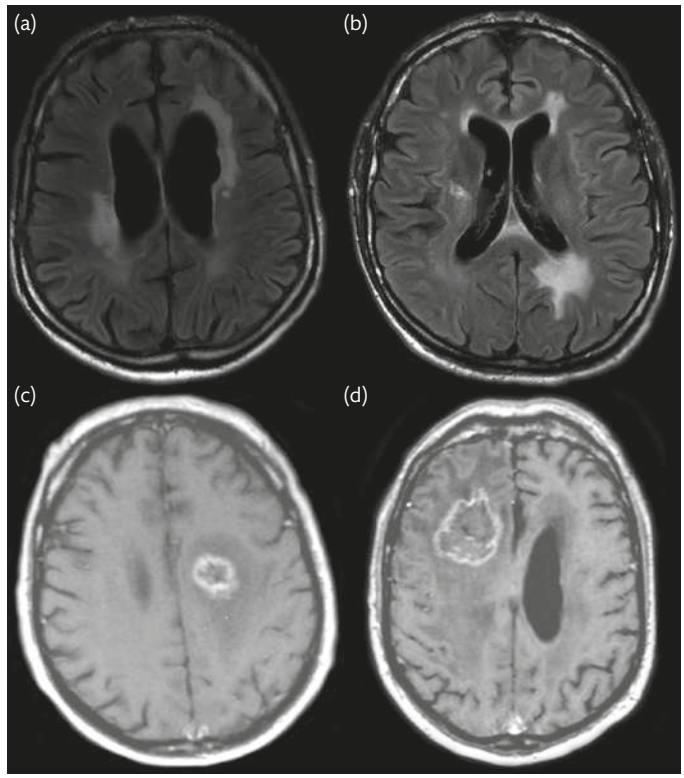

Figure 8.6 Magnetic resonance imaging abnormalities in patients with retinal vasculopathy with cerebral leukodystrophy and systemic manifestations.

(A, B) Axial gadolinium-enhanced fluid-attenuated inversion recovery images showing periventricular white matter lesions in two separate patients. (C, D) Axial gadolinium-enhanced T1-weighted images showing two mass lesions in the same patient, enhanced with gadolinium contrast and with surrounding oedema.

Pathophysiology of RVCL-S

When a *TREX1* mutation is found in a patient with symptoms suggestive of RVCL-S, the diagnosis is thereby confirmed. So far, all *TREX1* mutation carriers appear to develop the RVCL-S phenotype, indicating 100% penetrance (122). TREX1 is the most abundant 3′–5′ exonuclease in mammalian cells. Normal three prime repair exonuclease 1 (TREX1) protein resides in the cytoplasm in a protein complex attached to the endoplasmic reticulum (ER) membrane and likely translocates across the cell to clear products of DNA repair, replication, and retrotranscription (126,127). Truncating RVCL-S *TREX1* mutations result in mutant TREX1 that lacks the carboxyl terminus and can no longer bind to the ER membrane. While this mutant TREX1 retains its exonuclease activity, it is thought to lack proper subcellular context and to be located throughout the nucleus and cytoplasm (121). It is still unknown how the mutated TREX1 protein leads to a microvasculopathy.

TREX1 mutations have not only been found in RVCL-S, but also in Aicardi-Goutières Syndrome (AGS) (128,129), familial chilblain lupus (FCL) (130,131), and (neuropsychiatric) systemic lupus erythematosus (SLE) (132,133). *TREX1* consists of a catalytic domain, involved in enzymatic activity, and a C-terminal domain,

probably influencing the location of the TREX1 protein (114). Mutations in FCL and AGS are primarily found in the catalytic domain, while mutations in RVCL-S and SLE are most often found in the C-terminal domain. All RVCL-S-causing mutations that have been identified so far result in frameshifts and truncated TREX1. In AGS, FCL, and SLE, several types of mutations have been reported, including missense and frameshift mutations (134). The exact functional effects of these different types of mutations on these different locations of the *TREX1* gene remain to be elucidated.

As AGS, FCL, and SLE are all associated with a disruption of type 1 interferon (IFN) metabolism, this has incited research into the link between *TREX1* and (auto)immunity. Deficiency of TREX1 is postulated to cause accumulation of intracellular nucleic acids, which initiates an IFN-α-mediated innate immune response leading to inflammation and autoimmunity (135–137). Trex1-deficient mice have, for example, been shown to develop inflammatory myocarditis (138). A CSF lymphocytosis is common in patients with AGS, who are homozygous for *TREX1* mutations (128). More importantly, in patients with AGS expression of certain IFN-stimulated genes was found to be elevated in serum and CSF (139,140). In addition, a substantial increase in the release of pro-inflammatory cytokines (interleukin-6) and chemokines (C-X-C motif chemokine ligand 10 (CXCL10) and chemokine (C-C motif) ligand 5 (CCL5)) was detected (140). A similar IFN signature was described in a case report of a patient with RVCL-S, albeit using slightly different methods (141). Another recent study found that the carboxyl terminus of TREX1 is important in the regulation of oligosaccharyltransferase activity in the ER, and thereby in preventing glycan and glycosylation defects that can lead to immune disorders (142).

Autoimmune dysfunction in RVCL-S may lead to endothelial dysfunction, which has been suggested to occur in RVCL-S. Activation of the endothelium results in a pro-inflammatory, procoagulatory, and proliferative milieu (143). Clinical features of RVCL-S suggest the involvement of small vessels of several organs (vascular retinopathy, cerebral white matter lesions, and kidney and liver dysfunction). The presence of Raynaud's phenomenon points even more towards endothelial dysfunction. Both impaired endothelial-dependent vasodilatation and a mismatch between endothelium-derived vasoconstrictors (primarily endothelin-1) and vasodilators (primarily nitric oxide and prostacyclin) was demonstrated in Raynaud's phenomenon (144). Similar mechanisms may be involved in RVCL-S. A recent study demonstrated endothelial dysfunction in patients with RVCL-S and impaired endothelial independent vasoreactivity of dermal microvasculature in patients with CADASIL. An increased vascular stiffness is seen in both disorders (145). In addition, patients with RVCL-S had abnormal increased circulating levels of the markers of endothelial function—angiopoietin-2, and Von Willebrand Factor antigen and propeptide (146). A few studies in migraine also point towards endothelial dysfunction. Circulating endothelial progenitor cells (EPCs) are suggested to provide valuable information about endothelial regeneration capacity. Unfortunately, the cultured EPC type that probably best reflects 'real' EPCs has not been investigated in migraine (147). Circulating numbers and function of another EPC-like cell type have, however, been suggested to be reduced in migraine, meaning that patients with migraine may exhibit dysfunctional endothelial regeneration (148,149). Markers of endothelial activation were found to be increased in premenopausal women with migraine, and biomarkers of hypercoagulability and inflammation have also been associated with migraine in a population-based study (150–152). By unravelling overlapping mechanisms in the hypothesized endothelial dysfunction in RVCL-S and migraine, new pathophysiological mechanisms for both diseases may be revealed.

Small-vessel diseases associated with *COL4A1* mutations

A group of autosomal dominant syndromes in which the retinal and cerebral vasculature is also affected are the *COL4A1*-associated syndromes (153–155). *COL4A1* on chromosome 13 encodes the α1 chain of type IV collagen (COL4), which is a basement membrane protein that is also present in the vascular basement membrane. Co-occurrence of COL4A1 mutations and migraine has been described in a few studies.

Reported phenotypes of *COL4A1* mutation carriers are perinatal haemorrhage with porencephaly, and also sporadic late-onset intracerebral haemorrhages (156–160). HANAC syndrome (hereditary angiopathy, nephropathy, aneurysms, and muscle cramps) is a *COL4A1*-associated phenotype that has many systemic features. HANAC patients may have aneurysms within the intracranial segment of the internal carotid artery, muscle cramps, Raynaud's phenomenon, kidney defects, and cardiac arrhythmias (161). Another study suggested that *COL4A1* is associated with muscle–eye–brain/Walker–Warburg syndrome, which is characterized by ocular dysgenesis, neuronal migration defects, and congenital muscular dystrophy, and as such suggested that *COL4A1* may also play a role in cortical and muscular development (162). Ocular features in *COL4A1*-associated syndromes are variable and include retinal arteriolar tortuosity, cataracts, glaucoma, and anterior segment dysgenesis of the eye (the Axenfeld-Rieger anomaly) (154,163). Neurological symptoms include infantile hemiparesis (persistent, not intermittent), seizures, visual loss, dystonia, strokes, mental retardation, cognitive impairment, and dementia (155). A specific and curative treatment for the *COL4A1*-associated syndromes is not available.

Considering *COL4A1* mutations and migraine: a co-occurrence has been described in a few studies. One patient with MO and two relatives with unspecified migraine were described in a family with porencephaly (158). In a family with recurrent strokes and cataract without porencephaly, but with diffuse leukoencephalopathy and microhaemorrhages, one mutation carrier suffered from MA (164). MA was observed in three out of six mutation carriers in a family with hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy (165,166). As only 10 *COL4A1* mutation carriers with migraine have been described, without clear co-segregation in any of the families, this co-occurrence may well be coincidental. Although the *COL4A1*-associated syndromes show overlapping symptoms with the small-vessel diseases CADASIL and RVCL-S, the association with migraine is far less clear.

Imaging will reveal features such as diffuse leukoencephalopathy with the involvement of posterior periventricular areas, subcortical infarcts, cerebral microbleeds, and dilated perivascular spaces. In patients with porencephaly, large periventricular fluid-filled cavities are seen, and schizencephaly has also been observed (155,167). *COL4A1* screening can thus be considered when these features are seen on MRI, especially when ocular features are also present.

Mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke syndrome

In patients with migraine-like headaches in combination with episodes of hemiparesis at a young age, mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke (MELAS) syndrome should also be considered. MELAS is caused by mutations in mitochondrial DNA (mtDNA) and is maternally inherited (168). Early development is usually normal, but MELAS can manifest in childhood. Although the clinical criteria for MELAS used to include an onset of symptoms before the age of 40 years, an onset later in life has also been reported (169). Patients often experience a prodrome that resembles a migraine episode and consists of nausea, vomiting, throbbing headache, and abdominal complaints. The prodrome is followed by a sudden neurological deficit within hours or days. The neurological deficit can include hemiplegia, hemianopia, ataxia, or aphasia (170). In contrast to symptoms of (hemiplegic) migraine, the onset of the neurological deficit is sudden and the deficit is not (fully) reversible, causing patients to show progressive neurological dysfunction, including cognitive decline. In addition, patients can suffer from generalized seizures, muscle weakness, hearing loss, and a typical short stature (171–173).

In combination with the clinical findings, the diagnosis is primarily based on genetic testing. Mutations in several mtDNA genes have been found in MELAS, but most patients have a mutation in t*MT-TL1* (168,174). Because of skewed heteroplasmy, the mutation may not be found in leukocytes (175). After a negative genetic test result in blood, the pathogenic mutation may therefore still be detected in a biopsy of skin tissue or skeletal muscle, which can also reveal ragged red fibres. In addition, an elevated lactate can be demonstrated in blood and/or CSF (175).

Radiological imaging may reveal symmetric and progressive basal ganglia calcification, focal lesions, and, at a later stage, cerebral and cerebellar atrophy (170). Apart from white matter changes, deep grey matter changes have also been observed (176). The focal lesions do not always match a vascular territory, and may result from a mitochondrial cytopathy and angiopathy. A mitochondrial dysfunction may lead to energy depletion and neuronal necrosis (177). The occurrence of abnormal mitochondria and a respiratory chain deficiency have been demonstrated in the cerebral and cerebellar microvasculature of patients with MELAS, affecting not only the vascular smooth muscle cell layer, but also the endothelium (178,179). Because of the rather severe abnormalities on MRI, MELAS can be easily distinguished from other disorders, especially HM.

Neuronal and glial monogenic syndromes associated with migraine

The following monogenic syndromes do not always include migraine, but symptoms that mimic migraine or migraine auras may be present. The conditions are closely associated or even allelic with FHM1 and FHM2.

Episodic ataxia type 2

Episodic ataxia type 2 (EA2) is a rare disorder, characterized by attacks of ataxia lasting hours to days, accompanied by severe vertigo, nausea, and vomiting. A gaze-evoked, rebound, or downbeat nystagmus can occur not only during, but also in between attacks. A broad range of ictal symptoms, including dysarthria, tinnitus, dystonia, diplopia, and also hemiplegia and headache, may be present. Approximately 50% of patients with EA2 have migraine headaches (180). Cases with episodic hemiplegia have been described in a large EA2 family (181). Like HM, attacks usually start at a young age, during childhood or (early) adolescence (182,183). Stress, exertion, caffeine, and alcohol may precipitate attacks and patients often develop persistent cerebellar symptoms and cerebellar vermian atrophy (184). EA2 is caused by mutations in the FHM1 gene *CACNA1A*, which can not only be inherited autosomal dominantly, but also occur de novo (59,185–188). In EA2, missense mutations have been found in *CACNA1A*, and also deletions, leading to frameshifts and truncated proteins (189). In FHM1, *CACNA1A* mutations appear to result in a gain of function effect, while mutations in EA2 appear to lead to a loss-of-function effect (59). Patients with the recurring p.Arg1347Gln *CACNA1A* mutation may suffer from symptoms of both FHM and progressive ataxia, with temporary worsening after attacks, and also showed cerebellar atrophy (190). Although the exact molecular mechanisms may be different, there is thus marked clinical overlap of FHM1 and EA2.

Other findings that illustrate the overlap of episodic ataxia and HM are related to *SLC1A3*, which encodes the glial glutamate transporter excitatory amino acid transporter 1 (EAAT1). Mutations in this gene were found in patients with episodic ataxia, in a case with episodic ataxia, hemiplegia, and seizures, and in a case with pure HM (10,11,191). As functional studies demonstrated reduced glutamate uptake, involvement of the EAAT1 transporter could fit into the overall hypothesis that increased cerebral levels of K^+ and glutamate in the synaptic cleft increase neuronal excitability, leading to increased susceptibility to CSD. Episodic ataxia associated with *SLC1A3* mutations is designated as episodic ataxia type 6 (EA6) (191).

As in most subtypes of episodic ataxia, acetazolamide is often effective for reducing the frequency of EA2 attacks (180). In addition, a randomized controlled trial of 10 patients with EA, including seven patients with *CACNA1A* mutations, showed that the potassium channel blocker fampridine (4-aminopyridine, in a dosage of 5 mg three times daily) was significantly more effective in reducing attack frequency than placebo (192). In an earlier pilot study, fampridine completely prevented attacks of ataxia in two patients and markedly reduced attacks in one (193). Two of these patients had previously developed an increased frequency of attacks, despite treatment with acetazolamide (193). No trials have compared fampridine with acetazolamide in EA2.

Spinocerebellar ataxia type 6

Another disorder that is allelic with FHM1 is spinocerebellar ataxia type 6 (SCA6). Instead of point mutations that occur in FHM1 and also in EA2, SCA6 is associated with polymorphic, unstable, and expanded CAG repeats in exon 47 of *CACNA1A*. Patients carry 21–28 CAG triplets, compared with 4–16 in healthy individuals (194,195). Inheritance is autosomal dominant. A population-based study in England showed a point prevalence of 1.59 in 100,000 and the prevalence of the CAG repeat was approximately five in 100,000 (196). The SCA6 phenotype is characterized by a slowly progressive cerebellar ataxia, dysarthria, and nystagmus. The reported ages at onset vary between the second decade to even 70 years, which may differ significantly even among relatives with the same mutation, but

appears to be inversely correlated with the repeat length (197–199). The first symptoms are often complaints of gait unsteadiness and stumbling; sometimes a patient may first present with dysarthria. These symptoms may initially be episodic, at which stage there is marked overlap with the EA2 phenotype (200,201). The progression of symptoms is slow, but eventually all patients show gait ataxia, intention tremor, incoordination of the upper limbs, and dysarthria. Dysphagia is also rather common, as well as diplopia. A gaze-evoked or downbeat nystagmus may cause visual disturbances caused by difficulty fixating on moving objects (197,198). Cognitive function appears preserved in patients with SCA6 (202).

Although migraine does not appear to be particularly prevalent in patients with SCA6, a *CACNA1A* missense mutation was found in members of a family including several individuals with both progressive cerebellar ataxia and HM, and also individuals with progressive cerebellar ataxia alone, indicating the close association of the phenotypes (203).

MRI in patients with SCA6 has demonstrated atrophy of the cerebellar vermis and hemispheres, with sparing of the brainstem and cerebral cortex (197–199). Pathological examinations have revealed that the neurodegeneration is more widespread and also includes the cerebral cortex, thalamus, midbrain, pons, and medulla oblongata, but it is less severe than in other spinocerebellar ataxias (204). The cerebellar atrophy appears to result mainly from degeneration of Purkinje cells and, to a lesser extent, from granule cells (199,205). The neurodegeneration may be associated with cytoplasmic aggregations of the α_{1a} calcium channel protein (206).

The management of the disease is entirely supportive. Like in EA2, acetazolamide may help to eliminate episodes of ataxia. There are no treatments to delay or halt the progression of the disease. Patients with SCA6 have a normal life expectancy.

Alternating hemiplegia of childhood

Alternating hemiplegia of childhood (AHC) is an extremely rare disease (estimated incidence of one in one million births) and occurs before the age of 18 months. AHC is characterized by episodic hemiplegia or quadriplegia lasting a few minutes to several days. Other paroxysmal symptoms include tonic/dystonic attacks, nystagmus, strabismus, and dyspnoea. Typically, all symptoms disappear immediately on going to sleep, and may recur after awakening, in long-lasting attacks. Between the episodes, patients often show developmental delay, a learning disability, dystonia, ataxia, and choreoathetosis (207,208). When episodic hemiplegia occurs before the age of 18 months, AHC may be considered. A mutation in the FHM2 *ATP1A2* gene has been demonstrated in a patient with AHC, which suggested a close association with HM (209). Recently, however, mutations in *ATP1A3*, encoding the Na^+/K^+-ATPase α3 subunit, were discovered in AHC. Approximately 70% of patients carried an *ATP1A3* mutation, and genetic screening thus enables confirmation of AHC and differentiation from HM (210).

Mouse models of hemiplegic migraine and other monogenic migraine subtypes and syndromes

Mouse models have been developed for several monogenic diseases that are associated with migraine. The FHM1 mouse model's phenotype is very similar to the human FHM1 phenotype and has been studied extensively. The knock-in mouse models carry, for example, the human R192Q FHM1 *CACNA1A* mutation or the S218L FHM1 *CACNA1A* mutation (211,212). Knockdown *CACNA1A* mouse models can contribute to research into EA2 and SCA-6 (213). Homozygous FHM2 knock-out and knock-in mouse models were found to die immediately after birth, but heterozygous mice were viable (214,215). As increased susceptibility to CSD was demonstrated in the heterozygous knock-in mouse model, this model may be used for further in vivo research (215). Mouse models associated with the FHM3 *SCN1A* gene have so far only focused on the epilepsy phenotypes SMEI and GEFS+ (216,217). Transgenic mouse models for the vascular migraine models CADASIL and RVCL-S, but also mouse models with *COL4A1* mutations, have been developed as well (218,219). Although an association with *CSNK1D* and familial migraine (and advanced sleep phase) was reported only once, mice harbouring a *CSNK1D* mutation did exhibit a reduced threshold for CSD (9).

All these different mouse models are very useful to study genotype–phenotype correlations. Moreover, a translational research approach using monogenic human and mouse migraine models opens many possibilities for functional studies of migraine pathophysiology, aiming to develop new treatments in the future.

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9

Retinal migraine

Brian M. Grosberg and C. Mark Sollars

Introduction

Retinal migraine is characterized by attacks of monocular visual impairment associated with migraine headache. It is rare and poorly understood. Retinal migraine was first described by Xavier Galezowski in the late nineteenth century as 'ophthalmic megrim' (1). Since then, patients with monocular visual defects beginning before, during, or after attacks of otherwise typical migraine have been reported with various designations. Desmond Carroll introduced the term 'retinal migraine' to describe episodes of transient and permanent monocular visual loss in the absence of migraine headache (2). Subsequently, 'retinal migraine' has been applied to those cases of monocular visual impairment temporally associated with attacks of migraine. Noting that unilateral visual loss is not restricted exclusively to the retina, some advocated the term 'anterior visual pathway migraine' or 'ocular migraine' (3,4). The authors prefer the term 'migraine associated with monocular visual symptoms' because it distinguishes between the loss of vision in one homonymous hemifield and that of one eye and includes sites other than the retina, such as the choroid or the optic nerve.

Several definitions of retinal migraine have been proposed over the past 20 years. B. Todd Troost defined retinal migraine as a transient or permanent monocular visual disturbance accompanying a migraine attack or occurring in an individual with a strong history of migraine-like episodes (5). The International Headache Society established more rigorous criteria with the publication of the first edition of the International Classification of Headache Disorders (ICHD-1), which required at least two attacks of fully reversible monocular scotoma or blindness lasting less than 60 minutes associated with headache (type unspecified) (6). Criteria were revised in the 2018 third edition of the ICHD (ICHD-3) (**Box 9.1**) (7).

The literature includes positive and negative visual phenomena as symptoms of retinal migraine (8,9). Standard accounts of positive visual phenomena include flashing rays of light, zigzag lightning, and other teichopsia, whereas perceptions of halos, diagonal lines, and bright-coloured streaks are less commonly described (10,11). The negative visual losses include blurring, 'grey-outs', and 'black-outs', causing partial or complete blindness (12,13). Elementary forms of scotoma have been perceived as blank areas, black dots, or spots in the field of vision (14,15). Visual field defects can be altitudinal, quadrantic, central, or arcuate. Less frequently noted are complex patterns of monocular visual impairment, such as tunnel vision, the coalescence of peripherally located spots, and the appearance of 'black paint dripping down from the upper corner of my left eye' (16).

In most cases, the migraine headache was ipsilateral to the visual loss. Nearly 50% of patients with monocular visual loss had a history of migraine with typical visual aura. Rare cases of transient monocular visual loss have also been reported with cluster headache, idiopathic stabbing headache, chronic daily headache, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, and an unspecified headache type (17–21).

Recurrent monocular visual disturbances are strictly unilateral and without side shift in most patients, although some experience side-alternating attacks. The temporal relationship between the visual loss and the headache is variable. Usually, the onset of visual loss precedes or accompanies the headache; less often, the visual loss follows an attack of migraine headache. By definition, the visual symptoms occur within 1 hour of the headache. The duration of transient monocular visual loss vary widely between patients and within individual patients. The duration of the visual symptoms may be as short as a few seconds but usually last many minutes to 1 hour. Prolonged but fully reversible monocular visual loss rarely occurs, sometimes lasting hours, days, or even weeks (16,17,22–26). Only a few patients have had ophthalmological examinations during an attack. Examinations, when performed, were usually normal, suggesting retrobulbar involvement. One self-reported case of retinal migraine cited multiple ophthalmological examinations during attacks, as well as one performed by a retinal specialist (27). This patient was a 71-year-old male ophthalmologist who had suffered from attacks of migraine with and without aura since the age of 16 years. His conventional visual aura consisted of homonymous scintillating scotomas lasting 15–20 minutes. Beginning at the age of 56 years, he experienced recurrent monocular visual events, which were stereotypic, short-lived, and mostly isolated in nature. The patient reproduced the scotomas of some of these events using Amsler grids. With the exception of one episode, all of these events involved his left eye, lasted 10–11 minutes, and were not associated with headache. During one of these episodes, a retinal specialist examined him 6–7 minutes into the ictus. No evidence of retinal vasospasm, embolic phenomena, or other abnormalities was found.

Box 9.1 Criteria for the diagnosis of retinal migraine

A Attacks fulfilling criteria for 1.2 *Migraine with aura* and criterion B below.

B Aura characterized by both of the following:

1 Fully reversible, monocular, positive, and/or negative visual phenomena (e.g. scintillations, scotomata, or blindness) confirmed during an attack by either or both of the following:

a. Clinical visual field examination

b. The patient's drawing of a monocular field defect (made after clear instruction).

2 At least two of the following:

a. Spreading gradually over ≥5 minutes

b. Symptoms last 5–60 minutes

c. Accompanied, or followed within 60 minutes, by headache.

C Not better accounted for by another ICHD-3 diagnosis, and other causes of amaurosis fugax have been excluded.

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In nearly half of reported cases of retinal migraine, patients ultimately experienced permanent monocular visual defects, but no consistent pattern of visual field loss was noted. Severe narrowing or occlusion of retinal arteries and veins was observed rarely (1,2,17,23,28–39). The diagnoses of anterior or posterior ischaemic optic neuropathy were reported in about a dozen (4,40–50). Other findings included cotton wool spots (51), retinal pigmentary change (29), central retinal venous occlusion (52–54), central serous retinopathy, optic nerve atrophy (52), optic disc oedema (40), and haemorrhages of the optic nerve, retina, or vitreous (55,56).

Clinical vignette

A 44-year-old woman suffered from attacks of migraine without aura since the age of 30. The headaches began in the right nuchal and temple regions, typically lasted 1–2 days, and occurred an average of 1–2 times per month, usually in association with her menses. Associated features included photophobia, phonophobia, osmophobia, nausea, vomiting, facial pallor, and dysarthria. One year before presentation, the patient experienced 1–2 attacks per week of her otherwise typical migraine headache associated with recurrent bouts of monocular visual loss ipsilateral to the headache. Complete blindness of the right eye always began 30 minutes into the headache. Alternately covering each eye during attacks confirmed that the visual changes were limited to the right eye. The monocular visual loss lasted the entire duration of the headache, ranging from 8 hours to 3 days, and then fully resolved. There was a strong family history of migraine. Past history included asthma and abnormal uterine bleeding. The patient drank alcoholic beverages occasionally but denied cigarette smoking and illicit drug use.

Her general medical, ophthalmological, and neurological examinations were normal. Investigations included a computed tomography (CT) scan of the brain, magnetic resonance imaging (MRI) and magnetic resonance angiogram (MRA) of the brain, MRA of the neck, echocardiography, and extensive haematological tests, all of which were within normal limits. The patient was treated with topiramate 300 mg daily with complete cessation of her recurrent bouts of monocular visual loss, as well as a reduction of headaches.

Pathogenesis and pathophysiology

The underlying pathophysiology of retinal migraine remains largely unknown. Bouts of transient monocular visual loss lasting less than 1 hour, transient monocular visual loss of prolonged duration, and transient monocular visual loss that later becomes permanent correspond clinically to the typical visual aura of migraine, prolonged aura, and migrainous infarction, respectively. Perhaps these three phenomena affecting the cerebrum (especially the cortex) or the eye (especially the retina) share common pathophysiological mechanisms (9). Spreading depression of cortical neurons is the broadly accepted basis of the typical aura of migraine and perhaps a similar mechanism affects the retina. This phenomenon has been noted in the retina of the chicken (57). The expression of major *N*-methyl-D-aspartate receptor subtypes, NR1, NR2A, and NR2B (58), and calcitonin gene-related peptide receptors (59) in the chick retina makes them pertinent targets for pharmacological inhibition of spreading depression (58). One patient who described her transient monocular visual loss as black paint slowly dripping down from the corner of her monocular visual field may well be describing spreading depression of the retina.

Primary vascular dysregulation is associated with retinal vascular disease and is comorbid with migraine. Theoretically, it could be a factor in the pathogenesis of retinal migraine (60). Ischaemia is the other mechanism commonly invoked to explain permanent monocular visual loss in the setting of migraine. Vasospasm of retinal arterioles and veins has been demonstrated in cases of transient monocular visual loss, where no other predisposition to vascular disease was discovered (61,62). Vasospasm during migraine headaches has also been documented angiographically (63). Although vasospasm is no longer considered the primary cause of the focal neurological deficits of migraine, this older concept of migraine may account for the visual loss in some cases (9).

Some studies, such as kinetic arc perimetry (64), measurements with flickering light stimuli (65), motion coherence perimetry (66), and measurements of contrast thresholds for static and moving stimuli (67), implicated both cortical and precortical visual sites. A reduction in nerve fibre layer thickness has been found in migraine patients in contrast to control subjects (68). The significance of these findings to retinal migraine is uncertain.

Epidemiology

Retinal migraine is thought to be a rare disorder, but its true prevalence and incidence are unknown. In a review of the literature, Hill and associates applied strict International Headache Society criteria in a broad-based review of the reported cases of transient monocular visual loss, finding only five of 142 cases that met the definite criteria for retinal migraine. The authors attributed the other cases of transient monocular visual loss to retinal vasospasm (69,70). In another review, nearly two-thirds of patients with retinal migraine were found to be female (9). More than half of the patients experienced only transient monocular visual loss, whereas the remainder later developed permanent monocular visual loss in association with otherwise typical attacks of migraine. Men and women were equally affected in the transient group, whereas the permanent group showed

a female preponderance, with a female-to-male ratio of 2.5:1. Age at onset of retinal migraine ranged from 7 to 54 years. Mean age at onset was similar in both groups (24.7 years for the transient group, 23 years for the permanent group). The duration of retinal migraine before diagnosis ranged from days to several decades. Similarly, the evolution from transient to permanent attacks of monocular visual loss in the permanent group was variable, occurring within the same year of retinal migraine onset and up to 52 years later. With the exception of one case, in which attacks of transient monocular visual loss ceased after oral contraceptives were discontinued, no specific precipitating events were identified. Thirty per cent of patients had a documented family history of migraine. Because many cases did not include information on family history, this number may be underestimated. Only two patients had familial retinal migraine (71).

Minor risk factors for vascular disease were identified in only a few patients with transient and permanent monocular visual loss. They included hypertension, hyperthyroidism, pregnancy, diabetes, oral contraceptive use, smoking, and increased levels of factor VIII. These conditions were not thought to be the main cause of the visual loss (9).

Prevention

One treatment approach focuses on the avoidance of potential migraine triggers (i.e. stress, use of oral contraceptives, smoking) by patients with infrequent attacks. It has been suggested that prophylactic therapy should be deferred when patients have infrequent attacks, i.e. less than one attack per month (72). However, this course of action may not be prudent because episodes of permanent monocular visual loss can occur in migraineurs with and without prior attacks of transient monocular visual loss (73).

Differential diagnosis

Patients often have difficulty distinguishing between the loss of vision in one homonymous hemifield and the loss of vision in one eye. To make this distinction accurately, the patient must alternately cover each eye and compare their views. The description of hemifield loss with both eyes open is characteristic of a homonymous hemianopia rather than monocular visual loss. If monocular visual loss is confirmed, one must attempt to exclude other causes of transient or permanent monocular visual loss. The differential diagnosis of retinal migraine includes amaurosis fugax. In retinal migraine, visual loss typically evolves slowly and often lasts longer than amaurosis fugax of carotid artery origin. The 'shade dropping over a visual field', typical of micro-embolization, was not reported by patients with retinal migraine. Other causes of transient monocular visual loss include atherosclerosis; thrombus originating from the carotid artery, heart, or great vessels; giant cell arteritis; other vasculitic diseases with or without autoimmune diseases; primary vascular disease of the central retinal artery or vein; illicit drug use; demyelinating disease; and hypercoagulable states, such as macroglobulinaemia, polycythaemia, anticardiolipin antibody syndrome, and sickle cell disease. Less common causes are orbital diseases, including mass lesions, retinal detachment, and intermittent angle-closure glaucoma (9,74).

Diagnostic work-up

The clinician needs to identify or exclude secondary causes of transient monocular blindness because retinal migraine is a diagnosis of exclusion (see Table 9.1). If a patient's history or general physical, ophthalmological, or neurological examination includes atypical features, imaging studies or other diagnostic testing are warranted. Features that should prompt concern for an underlying secondary cause of headache with transient monocular blindness include absence of a typical migraine history, onset after the age of 50 years, incomplete resolution of monocular visual loss, concomitant medical problems that can precipitate attacks of transient monocular blindness, and the presence of atypical neurological signs or symptoms. All cases with persistent monocular visual loss should be fully investigated. To exclude the possibility of a cardio-embolism, investigations such as electrocardiography, echocardiography, and Holter monitoring need to be performed. Diagnostic testing of patients with suspected ischaemic disease of the eye or brain should include duplex ultrasound, CT, MRI and MRA, fluorescein angiography, and, in uncertain cases, conventional catheter angiography. Neuroimaging can exclude an orbital or intracranial mass. Other diagnostic possibilities, such as vasculitis, hypercoagulable states, illicit drug use, and rheumatological disorders, require a complete laboratory evaluation, consisting of a complete blood count with differential and platelet count, prothrombin time, partial thromboplastin time, toxic drug screen, lupus anticoagulant and anticardiolipin antibody levels, erythrocyte sedimentation rate, rheumatoid factor, antinuclear antibody titre, antiphospholipid antibodies, protein C and S, antithrombin III levels, and serum protein electrophoresis (73).

Prognosis and complications

Although retinal migraine has traditionally been viewed as a benign condition, it appears that patients with migraine may have subclinical precortical visual dysfunction and permanent attacks of partial

Table 9.1 Clinical factors favouring retinal migraine versus other causes of monocular visual loss.

Factors favouring other diseases	Factors favouring retinal migraine
Age ≥ 50 years	Age ≤40 years
No history of migraine	History of migraine
PMVL	Migraine with TMVL
Hypercoagulable state	TMVL
Embolic source	
Drugs (OCPs, cocaine)	
Increased intracranial pressure	
Atypical neurological signs	
Vascular disease • Dissection • Occlusion • Vasculitis	

PMVL, permanent monocular visual loss; TMVL, transient monocular visual loss; OCPs, oral contraceptive pills.

or complete monocular visual loss occur more often than generally appreciated. Studies with automated perimetry have demonstrated subclinical visual field defects in some asymptomatic patients with migraine (75). There was a correlation between these findings and duration of disease and advancing age.

Some patients with retinal migraine who experience transient monocular visual loss may present with considerable variation in phenotype (either continuing to have transient visual loss or experiencing new attacks of permanent visual loss), whereas others only experience permanent monocular visual loss without a pre-existing history of transient visual loss. No specific factor has been identified to account for this variation in phenotype or for the heterogeneity of this condition (73). Just as migraine aura sometimes gives rise to migrainous infarction, the authors believe that irreversible visual loss is part of the spectrum of retinal migraine and perhaps a form of migrainous infarction.

Patients with retinal migraine appear to have prolonged and permanent monocular visual loss much more commonly than those with migraine who experience prolonged typical aura or migrainous infarction. The high number of patients with transient monocular visual loss who eventually develop permanent monocular visual loss makes retinal migraine a less benign condition than migraine with typical visual aura. Therefore, although there are no data to determine the efficacy of preventive treatment for this entity, preventive drug therapy seems prudent, even if attacks are infrequent (9).

Management

No clear guidelines exist regarding the management of patients with retinal migraine. In an attempt to prevent irreversible ocular damage, early medical management with daily aspirin and a migraine preventive agent may be advisable (73). Prophylactic medications that anecdotally have provided benefit include calcium channel blockers (i.e. verapamil, nifedipine, nimodipine), tricyclic antidepressants (i.e. nortriptyline), beta blockers (i.e. propranolol), and neuromodulators (i.e. divalproex sodium, topiramate). Aspirin is a logical agent because of its antiplatelet activity. In a few cases, simple monotherapy reduced the frequency of migraine with and without monocular visual defects. The authors favour antiepileptic drugs (i.e. topiramate or divalproex sodium) and tricyclic antidepressants (i.e. amitriptyline or nortriptyline). Although some patients respond to beta blockers, we do not usually recommend beta blockers because of their theoretical potential for arteriolar constriction. Although episodes of vasospastic amaurosis fugax appear to have been successfully treated with calcium channel blockers (76), they were not effective in the few patients the authors treated. Several patients, unfortunately, were refractory to many migraine preventive medications given as monotherapy or in combination.

There is currently insufficient clinical information to support specific recommendations for acute medical therapy in the treatment of retinal migraine. Given the potential risk of worsening any underlying vasospasm, medications with vasoconstrictive properties (i.e. ergotamines, triptans) should not be used (73). Only a few patients were treated with acute medication during the attack of retinal migraine. Inhaled carbon dioxide improved vision 'slightly' in a single patient during a single attack, whereas amyl nitrate and isoproterenol via inhaler showed 'good efficacy' in improving the visual loss in a few patients. None of these medications helped relieve the headache (77,78). Patients who experienced permanent monocular visual loss showed no consistent benefit from calcium channel blockers, oral and intravenous corticosteroids, or vasodilators.

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10

Migraine, stroke, and the heart

Simona Sacco and Antonio Carolei

Migraine and stroke

Accumulating data have linked migraine to stroke. The relationship between migraine and stroke is complex and bidirectional (1,2). A stroke, either ischaemic or haemorrhagic, may produce symptoms mimicking a migraine attack; a migraine attack may mimic a stroke; migraine may be directly associated with an ischaemic stroke (migrainous infarction); migraine may represent a risk factor for stroke; several diseases, mostly genetically determined, include among their clinical manifestations attacks of migraine and stroke; lastly, migraine has been associated with subclinical infarct-like brain lesions and white matter hyperintensities.

A stroke, either ischaemic or haemorrhagic, may produce symptoms mimicking a migraine attack (see also Chapter 37). A migraine-like headache may occur especially when lesions are located in the posterior circulation, in cortical areas, or when the ischaemic event is caused by an arterial dissection (3–6). In these instances the headache should not be diagnosed as migraine, but rather as a secondary headache and coded according to the International Classification of Headache Disorders, 3rd edition, (ICHD-3) as 'Headache attributed to ischaemic stroke or transient ischaemic attack' (code 6.1) or 'Headache attributed to non-traumatic intracranial haemorrhage' (code 6.2) (7). In those secondary headaches, the pain develops in close temporal relationship with other symptoms and/or clinical signs of the vascular event or leads to its diagnosis and improves in parallel with stabilization or amelioration of other symptoms or clinical or radiological signs of the vascular event (7). In patients with a previous history of migraine, the onset of a stroke may trigger an acute attack (8); in these circumstances the symptom should not be misinterpreted as being involved in the mechanism of ischaemia (9). Likewise, cases of migraine that resolved or ameliorated after stroke have also been reported.

A migraine attack may also mimic a stroke. In fact, aura symptoms resemble the symptoms of transient ischaemic attack (TIA) (10). Differential diagnosis may be challenging when the aura occurs for the first time, when it is not followed by headache, or when it affects older patients. The mode of onset is crucial: the focal deficit is typically sudden in a TIA and with a slower evolution and a serial progression of symptoms in a migrainous aura. Furthermore, positive phenomena such as scintillating scotoma or paraesthesia are far more common in migrainous aura than in TIA, whereas negative phenomena are more usual in TIA. When people present with symptoms of an aura that persists much longer than usual, magnetic resonance imaging (MRI) of the brain may be required to differentiate between an acute infarction and a persistent aura. Hemiplegic migraine and basilar migraine also pose a challenge to the appropriate diagnosis as they can resemble an acute stroke.

Migraine may be directly associated with an ischaemic stroke (migrainous infarction; ICHD-3 code 1.4.3) (see also Chapter 37) (7,11). This condition is very rare, with an estimated incidence of 0.8 per 100,000 cases annually (12), but in the past, before the development of the ICHD diagnostic criteria, it was vastly overestimated. Epidemiological studies have shown that 0.5–1.5% of all ischaemic strokes are migrainous infarctions; in younger patients, migrainous infarction was reported to account for 13% of first-ever ischemic strokes (12–15). Migrainous infarction can be diagnosed only in patients with a definite history of migraine with aura (MA). To meet the diagnostic criteria, the stroke must occur during a migraine attack that is typical of previous attacks, except for the persistence for more than 60 minutes of one or more of the aura symptoms; brain neuroimaging must demonstrate an ischaemic infarction in a relevant cerebral area (**Figure 10.1**), and the clinical condition must not be attributed to another disorder, even though stroke risk factors may be present (7). In patients with migrainous infarction, symptoms are visual in 82.3%, sensory in 41.2%, and dysphasic in 5.9% (16). If a concomitant aetiology is detected (e.g. cervical arterial dissection), or if a patient with a history of migraine without aura (MO) develops an ischaemic stroke after a migraine attack, the disease cannot be classified as migrainous infarction. As most strokes in migraineurs occur outside the migraine attacks, only a minority of ischaemic strokes in migraineurs meets these criteria. Migrainous infarctions usually occur in young people, are mild at onset, and the corresponding lesions are located mainly in the posterior circulation territory (16,17). The prognosis in terms of survival and functional outcome is usually good. A high prevalence (64.7%) of patent foramen ovale in those with migrainous infarction has been reported (16), but the causal link is not clear. The pathogenesis of an infarction is probably related to severe hypoperfusion occurring during the aura phase, even though the precise causative mechanism remains to be established. After a migrainous stroke ergotamine or triptans use should be avoided (18).

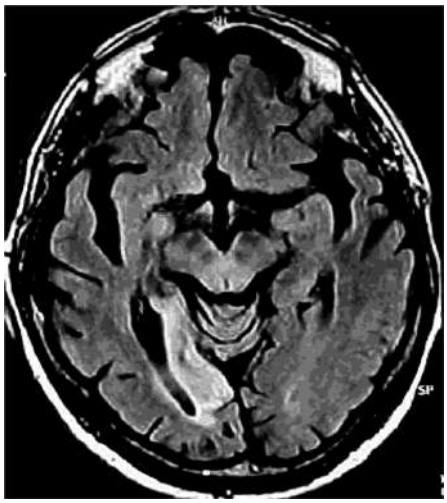

Figure 10.1 Brain magnetic resonance imaging showing a migrainous infarction in a patient diagnosed with migraine with aura who presented a persisting right hemianopia.

Courtesy of Stefano Bastianello, Professor of Neuroradiology, University of Pavia, Italy.

Migraine is also a risk factor for stroke (**Box 10.1**), as a large body of published data indicates an increased risk of ischaemic stroke in migraineurs, illustrated in three meta-analyses (**Table 10.1**) (19–21). All of them found a significant increase in the risk of ischaemic stroke in patients with any migraine, with a pooled adjusted effect estimate between 1.73 and 2.16 (**Table 10.1**) (19–21). Whereas this increased risk has been statistically proven in MA, only a non-significant trend towards the association has been observed in MO. The American Migraine Prevalence and Prevention study (AMPP), a population-based investigation involving 120,000 US households (22), which became available only after the publication of the aforementioned meta-analyses (19–21), confirmed the above reported evidence. In detail, the AMPP study found an association between any migraine and ischaemic stroke and between MA and ischaemic stroke, but no association between MO and ischaemic stroke (22). More recently, the Northern Manhattan Study (NOMAS), a prospective population-based study including 1292 participants with a mean age of 68 years followed for a mean of 11 years, evaluated the possible association between migraine and cardiovascular events, including stroke (23). The study was unable to demonstrate an association between migraine, either MA or MO, and stroke (23). Notably, the authors found that migraineurs, as compared to non-migraineurs, had an increased risk of stroke if they were also current smokers (23). A further study including 1,566,952 children aged 2–17 years was unable to demonstrate an association between migraine and ischaemic stroke in the same age group (24). Besides, a post-hoc analysis of the same adolescents showed a threefold increased risk of ischaemic stroke among those with migraine (24). A recent additional study based on administrative coding data of nearly 50,000 patients hospitalized for a first stroke indicated an increased risk of ischaemic stroke in migraineurs versus non-migraineurs (25). The Oxford Vascular Study (OXVASC), a population-based study including 1810 participants with TIA or ischaemic stroke, showed that as compared to events with determined aetiology, patients with cryptogenic events most often had a history of migraine. The same association was seen for MA and MO in an analysis stratified by sex and vascular territory (26). In this study, as expected, the frequency of migraine decreased with age in the overall cohort; however, the frequency of history of migraine did not fall with age in patients with cryptogenic TIA or stroke, such that with an analysis stratified by age, the association of migraine and cryptogenic events was strongest at older ages (26). The Italian Project on Stroke in Young Adults (IPSYS) demonstrated that in young patients with ischaemic stroke, MA represented an independent risk factor of overall recurrent vascular events and of recurrent ischaemic stroke (27).

Intriguingly, the severity of a migraine attack is not associated with an increased risk of ischaemic stroke; on the contrary, a high frequency of attacks (>12 attacks per year) and a recent onset of migraine (lifetime duration of <1 year before the stroke event) have been related to an increased risk (28,29). As the early studies focused on women (30–32), there exists a huge body of evidence linking ischaemic stroke with migraine in women; data on migraine in men are scarce and lacking in detail. As no direct estimates of the risk in men versus women are available, it is impossible to establish whether it is higher in one sex. Also, the risk of having a TIA seems to be increased in migraineurs, although this issue has not been extensively investigated. Misdiagnosis of migrainous aura as TIA may represent a limitation in the proper study of this association. In a case–control study, women with MA versus non-migrainous women had a twofold increase in the risk of having a TIA; this was confirmed by data from the Women's Health Study (WHS) (30,33). Only one of the aforementioned studies found an increased risk of TIA in women who had MO instead of MA (30).

Several studies also addressed the possible association between migraine and haemorrhagic stroke, but with conflicting results. A meta-analysis of those studies disclosed a significant association between the two conditions (**Table 10.1**) (34). The risk of haemorrhagic stroke increased by 50% in patients with any migraine versus non-migraineurs. The overall risk of haemorrhagic stroke, however, was lower than that reported for ischaemic stroke in other meta-analyses (19–21). The risk of haemorrhagic stroke was increased when female migraineurs of any age and female migraineurs aged <45 years were compared with control subjects. The meta-analysis could not prove an association of either MA or MO with an increased risk of haemorrhagic stroke, as only three studies collected data on the risk of haemorrhagic stroke according to migraine type (35–37). Two of these studies showed an association between MA and haemorrhagic stroke (36,37), while only one of them showed an association between MO and haemorrhagic stroke (37). However, as MA was the smaller subgroup and the effect size estimate was higher than that for MO, the meta-analysis might have had insufficient power to detect a possible association. Regarding haemorrhagic stroke type, available data suggest that the association between migraine and haemorrhagic stroke is driven by an increase of intracerebral, but not subarachnoid, events (36). Other authors performed a case–control study using data from 1797 patients with intracerebral haemorrhage and 1340 patients with subarachnoid haemorrhage and frequency-matched controls from a large epidemiological dataset, The Health Improvement Network (THIN) (38). In this study, the authors were unable to demonstrate an increased risk of overall haemorrhagic stroke or of intracerebral haemorrhage or subarachnoid haemorrhage in those with migraine versus non-migraineurs. The analysis performed according to migraine type showed that neither MA nor MO were associated with

Box 10.1 Evidence referring to the association between migraine and the risk of vascular disease

Ischaemic stroke
- Numerous studies have demonstrated an association with any migraine.
- Definite association with migraine with aura (MA).
- No definite association with migraine without aura (MO).
- Association with MA confirmed by three meta-analyses.

Transient ischaemic attack
- The risk seems to be increased in migraineurs, although this issue has not been extensively investigated owing to a challenging overlap of symptoms with migraine aura.

Haemorrhagic stroke
- Several studies have addressed the topic and provided inconsistent results.
- A meta-analysis of those studies indicated a small but significant association.
- No definite conclusion regarding migraine type.

Cardiac events
- Two large studies have indicated an association with any migraine in men and women and with MA in women (data not available for men).
- An additional study has reported an association between migraine (any migraine, MA, and MO) and myocardial infarction.
- Conflicting results provided by other available studies.
- Association with migraine confirmed in a meta-analysis.

Vascular death
- A meta-analysis and a large study have supported an association with MA.
- No association with any migraine according to meta-analysis of data.

Other vascular diseases
- Studies indicated a possible association with any migraine and retinal disease and peripheral artery disease.

Brain lesions
- Migraine has been associated with white matter hyperintensities and infarct-like lesions.
- Association of migraine with white matter hyperintensities has been confirmed in two meta-analyses.

Adapted from *The Journal of Headache and Pain*, 14, 80, Sacco S, Ripa P, Grassi D et al., Peripheral vascular dysfunction in migraine: a review. © Sacco et al.; licensee Springer, 2013. This article is published under license to BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0). Doi: [10.1186/1129-2377-14-80].

an increased risk of haemorrhagic stroke. Only patients with a long history (≥20 years) of migraine had an increased risk of intracerebral haemorrhage versus control subjects. The already reported study including 1,566,952 children aged 2–17 years was unable to demonstrate an association between migraine and haemorrhagic stroke (38). Another recent study did not demonstrate an increased risk of haemorrhagic stroke in migraineurs; however, in this same study the subanalysis by sex suggested an increased risk for haemorrhagic stroke in women migraineurs versus non-migraineurs but no difference by migraine status in men (25).

There are several diseases, mostly genetically determined, that include among their clinical manifestations migraine and cerebrovascular events (39). The best known of those diseases is cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) (**Figure 10.2**), although other conditions have also been recognized and are listed in **Table 10.2** (see also Chapter 8) (40–44).

Migraine has also been associated with subclinical infarct-like brain lesions and white matter hyperintensities (**Figures 10.3 and 10.4**) (45–49). Infarct-like lesions appear as small infarcts on brain MRI mostly in the absence of a clinical history of stroke. Their exact nature still remains elusive, as some of them may represent enlarged perivascular spaces or, alternatively, might be of a different nature than ischaemic. Even in this case, data point toward a clear association with MA, while data referring to any migraine or MO are controversial (46–50). The Cerebral Abnormalities in Migraine, and Epidemiological Risk Analysis (CAMERA) study showed that subjects with migraine had a sevenfold increased risk for infarct-like lesions in the cerebellum compared with controls, an association that was stronger for patients with MA and for those with a high attack frequency (46,47). Those findings are in agreement with the Reykjavik study, which found that women with MA in mid-life had an increased risk of cerebellar infarct-like lesions in later life (49). In that study, the risk was independent of the presence of cardiovascular risk factors. In the Epidemiology of Vascular Aging (EVA) study, participants with MA had over a threefold increased risk of brain infarcts (48). Furthermore, there was a suggestion that participants with MA were at increased risk of multiple infarcts (48). Data from the NOMAS indicated that participants reporting migraine overall had double the odds of infarct-like lesions (odds ratio 2.1; 95% confidence interval 1.0–4.2) when compared with those reporting no migraine (51). Recently, data from the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER), a placebo-controlled trial assessing effects of pravastatin on cardiovascular disease, showed no association between migraine (either MA or MO) and infarct-like lesions (52). The 9-year follow-up data from the CAMERA study found that migraine was not associated with the progression of infarct-like lesions (53). Available evidence mostly suggests that infarct-like lesions are particularly common in the posterior circulation and cerebellar border zone (54–57). At variance, the results of the EVA study indicated that most of the infarcts were located outside of the cerebellum or the brainstem (48). White matter abnormalities in migraineurs have an uncertain clinical significance. Their pathological correlates may correspond to gliosis, demyelination, and loss of axons; this set of findings has been attributed to microvascular damage. Prevalence of white matter abnormalities in migraineurs ranges from 4% to 59% (58). Regarding white matter hyperintensities, the CAMERA study indicated that in women the prevalence of deep white matter abnormalities was higher in migraineurs than controls (46). The association was independent of the presence or absence of aura and the risk increased with attack frequency. In men, deep white matter abnormalities were not influenced by the presence, subtype, or frequency of migraine. The EVA study confirmed the association of migraine with white matter abnormalities (48). The association with deep white matter abnormalities was stronger for MA than MO. The association was not specific to migraine headaches but extended to non-migraine headaches, especially tension-type headaches. The meta-analysis of available studies showed an association between white matter abnormalities and MA and no association with MO (**Table 10.1**) (58). More recently, data from the NOMAS indicated no association between MA or MO and

Table 10.1 Risk of cardiovascular diseases in migraineurs according to the available meta-analyses

	Any migraine vs control	Migraine with aura vs control	Migraine without aura vs control
Ischaemic stroke			
Etminan et al., 2005 (19)	2.16 (1.89-2.48)	2.88 (1.89-4.39)	1.56 (1.03-2.36)
Schürks et al., 2009 (20)	1.73 (1.31-2.29)	2.16 (1.53-3.03)	1.23 (0.90-1.69)
Spector et al., 2010 (21)	2.04 (1.72-2.43)	2.25 (1.53-3.33)	1.24 (0.86-1.79)
Haemorrhagic stroke			
Sacco et al., 2013 (34)	1.48 (1.16-1.88)	1.62 (0.87-3.03)	1.39 (0.74-2.62)
Myocardial infarction			
Schürks et al., 2009 (20)	1.12 (0.95-1.32)	–	–
Sacco et al., 2015 (64)	1.33 (1.08-1.64)	2.61 (1.86-3.65)	1.14 (0.81-2.45)
Angina			
Sacco et al., 2015 (64)	1.29 (1.17-1.43)	2.94 (1.59.5.43)	1.45 (1.06-2.00)
Vascular death			
Schürks et al., 2009 (20)	1.03 (0.79-1.34)	–	–
Schürks et al., 2011 (61)	1.09 (0.89-1.32)	–	–
Stroke-like lesions			
Bashir et., 2013 (58)	–	1.07 (0.87-1.33)	0.76 (0.56-1.03)
White matter hyperintensities			
Swartz et., 2004	3.9 (2.26-6.72)	–	–
Bashir et., 2013 (58)	–	1.68 (1.07-2.65)	1.34 (0.96-1.87)

Data are effect size (95% confidence interval)

white matter hyperintensity volume (51). A further analysis of data from a subset of 506 participants included in the PROSPER study was unable to demonstrate an association between migraine either MA or MO and white matter hyperintensities (52). The 9-year follow-up data from the CAMERA study found that migraine was associated with significantly greater white matter abnormality progression in women (53). Progression of white matter hyperintensities was not associated with attack frequency, duration, or severity, or antimigraine therapy (53). At variance, a further recent population-based study showed that migraine is associated with white matter hyperintensities cross-sectionally but not with their progression over time (45). The available studies do not support that migraineurs with white matter abnormalities are at risk of cognitive impairment (48,53,59). A further analysis of data from the PROSPER study was unable to demonstrate any association between overall migraine with cerebral microbleeds (52). However, analysis stratified by migraine type and cerebral microbleeds location (lobar, basal ganglia, infratentorial) indicated an association between MO with infratentorial microbleeds (52).

Migraine and cardiovascular diseases

The risk of cardiac events in migraineurs varies greatly among studies, ranging from a lower-than-average to a moderately increased risk (20,50). A major limitation is represented by the availability of data disaggregated for migraine type only from two studies (22,60). With those limitations, evidences suggest an increased risk of myocardial infarction (MI) in patients with MA, while no conclusion can be drawn referring to any migraine and MO. A meta-analysis did not show an increased risk of MI in patients with any migraine versus no migraine (Table 10.1) (20). In fact, only one of the studies included in the meta-analysis reported disaggregated data for migraine type (60); in that study, which was part of the WHS, at the end of a mean 10-year follow-up, MO was not associated with an increased risk of any vascular event, whereas MA was associated with an increased risk of MI, coronary revascularization, angina, and death due to vascular disease. After the publication of the aforementioned meta-analysis (20), the AMPP study found an association between migraine (any migraine, MA, and MO) and MI (22). A further meta-analysis showed that the presence of any migraine did not alter the risk of coronary artery disease mortality (61); only MA increased the risk of coronary artery disease mortality (62). In addition some data are reported on the association of migraine with angina. A cohort of >12,000 individuals participating in the Atherosclerosis Risk in Communities (ARIC) study found an association between migraine (particularly MA) with Rose angina that, in the absence of a corresponding association with coronary artery disease, suggested that the association between migraine and angina was not mediated by coronary artery disease (63). However, the ARIC study did not allow for a definite conclusion, mostly because of a possible bias related to the assessment of the headaches. A more recent meta-analysis indicated a 30% increase in the risk of MI in patients with migraine versus non-migraineurs (Table 10.1) (64). The analysis stratified according to aura status indicated an increased risk of MI in patients with MA versus non-migraineurs, while the meta-analysis was unable to show an increased risk of MI in those with MO (64). This same meta-analysis also indicated that migraineurs versus non-migraineurs had an increased risk of angina (64). In the case of angina, the risk was increased in both migraineurs with MA and MO (64). Both for MI and angina, the meta-analysis indicated that the overall increased risk was mostly driven by the

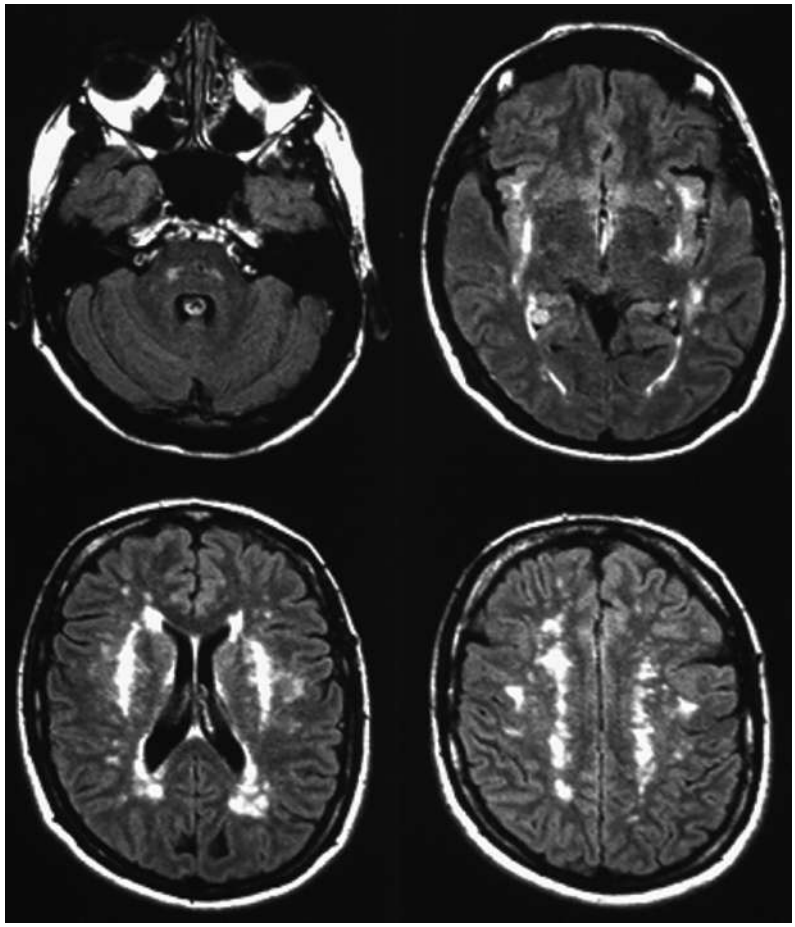

Figure 10.2 Brain magnetic resonance showing white matter hyperintensities in a patient diagnosed with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).
Courtesy of Stefano Bastianello, Professor of Neuroradiology, University of Pavia, Italy.

Table 10.2 Genetic diseases including among their clinical features stroke and migraine

Disease	Genetics	Clinical features
Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	Mutation of the *NOTCH3* on chromosome 19	Attacks of migraine with and without aura, mood disturbances, transient ischaemic attacks or strokes (usually lacunar infarcts), progressive cognitive decline; less common clinical features are epilepsy, acute reversible encephalopathy, and myopathy
Mitochondrial encephalopathy lactic acidosis with stroke-like episodes (MELAS)	Mutation at position 3243 of the mitochondrial genome	Seizures, encephalopathy, stroke-like episodes, migraine mostly associated with vomiting and aura, short stature, cognitive impairment, depression, cardiomyopathy, cardiac conduction defects, and diabetes mellitus
Autosomal-dominant retinal vasculopathy with cerebral leukodystrophy (AD-RVCL)	Mutation of *TREX1* on chromosome 3	Systemic microvasculopathy with adult-onset retinal vasculopathy and cerebrovascular disease variably associated with migraine, mainly without aura
Hereditary infantile hemiparesis, retinal arteriolar tortuosity and leukoencephalopathy (HIHRATL)	Mutation *COL4A1* on chromosome 13	Cerebral small-vessel disease, including subcortical haemorrhagic and ischaemic lacunar strokes and leukoaraiosis. Patients usually suffer also from migraine, mostly MA, seizures, infantile hemiparesis, developmental delay, neuropsychological abnormalities, and ocular, renal and cardiac involvement

MA, migraine with aura.

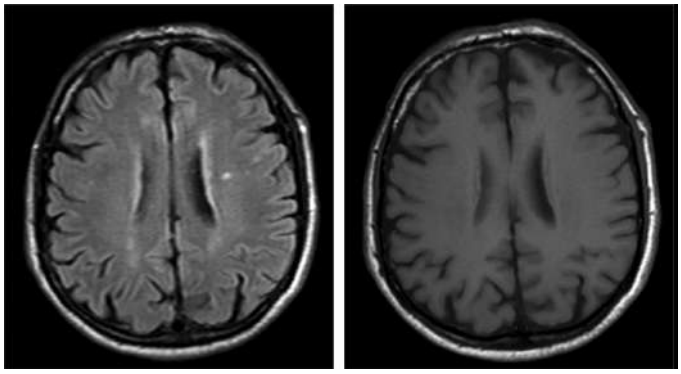

Figure 10.3 White matter hyperintensities in a patient with migraine headache. They are small, punctate lesions in the deep and periventricular structures. They appear as hyperintense on fluid-attenuated inversion recovery (left image) and T2 sequences, and hypointense on T1 sequences (right image).
Courtesy of Stefano Bastianello, Professor of Neuroradiology, University of Pavia, Italy.

association in women, while the meta-analysis was unable to demonstrate the same association in men (64).

Mechanisms linking migraine to cardiovascular diseases

The mechanisms underlying the relationship between migraine and cardiovascular diseases are cryptic and there are possible hypotheses (Figure 10.5). Concerns were raised on an increased vascular risk attributable to the different pharmacological agents used to treat migraine that might be responsible for the increased cardiovascular risk in migraineurs. The concerns particularly included triptans and compounds containing ergotamine because of their vasoconstrictive properties. However, neither ergots nor triptans have been consistently linked to an increased risk of stroke or other ischaemic events, at least when taken at recommended doses (65,66). Moreover, as MO and MA are similarly treated and the data on the association between migraine and stroke refer to the pretriptans era, the hypothesis seems even more unlikely. Concerns have also been raised on the vascular safety of non-steroidal anti-inflammatory drugs. A recent network meta-analysis concluded that although uncertainty remains, little evidence exists to suggest that any of the investigated drugs are not safe in cardiovascular terms (67). Comorbid conditions may complicate matters further. Migraine is positively related to anxiety and depression (68), which, in turn, are positively related to cardiovascular diseases (69).

A higher burden of comorbid vascular risk factors in migraineurs than in non-migraineurs has been reported by some studies and used to explain the increased cardiovascular risk (70). In these studies migraineurs were more likely to have an unfavourable cholesterol profile; to have elevated blood pressure; to have an increase in total cholesterol, non-high-density lipoprotein cholesterol, apolipoprotein B100, C-reactive protein and/or body mass index; to report a history of early-onset coronary heart disease or stroke; to have had an elevated Framingham risk score; to use oral contraceptives; and to have the methylenetetrahydrofolate reductase (*MTHFR*) C677T genotype (70–75). However, in most of the studies that found an association between migraine and cardiovascular disease, at least the conventional vascular risk factors were present in the multivariate model that showed the association (76). Any increased burden of conventional vascular risk factors in migraineurs would have led to an increased atherothrombotic load, but, as already reported, no such increase has been documented and there is actually evidence for the contrary (33,63,77,78). Several studies indicated that the migraine–stroke association was present in the absence of traditional vascular risk factors and that the type of stroke was less frequently a large-vessel stroke or a small-vessel stroke when compared with strokes in the general stroke population (29,33). Cardiac events observed in migraineurs did not seem to be attributable to atherothrombosis. The ARIC study, having found that migraine was associated with Rose angina, but not with coronary artery disease, proposed a generalized vasospastic disorder as a putative mechanism underlying both migraine and angina (63). This hypothesis was further supported by the finding that in women

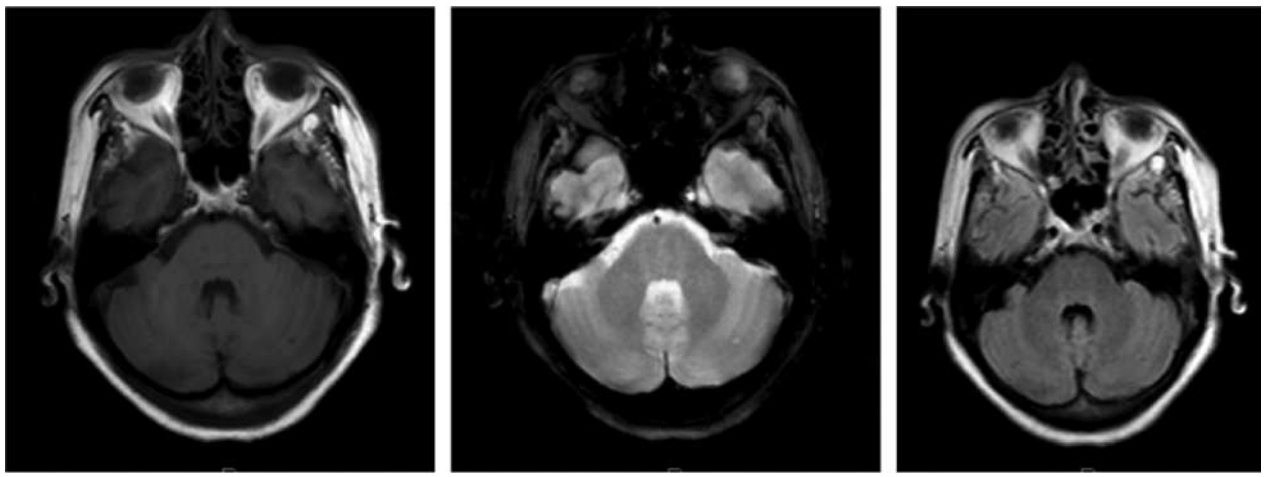

Figure 10.4 Infarct-like lesion in a patient with migraine. A brain infarct appears as focal lesions of ≥3 mm with the same signal characteristics as cerebrospinal fluid on T1 (left image), T2 (central image), and fluid-attenuated inversion recovery (right image) sequences. Infarct-like lesions can be discriminated from dilated vascular space (Virchow-Robin space) according to their shapes and locations.
Courtesy of Stefano Bastianello, Professor of Neuroradiology, University of Pavia, Italy.

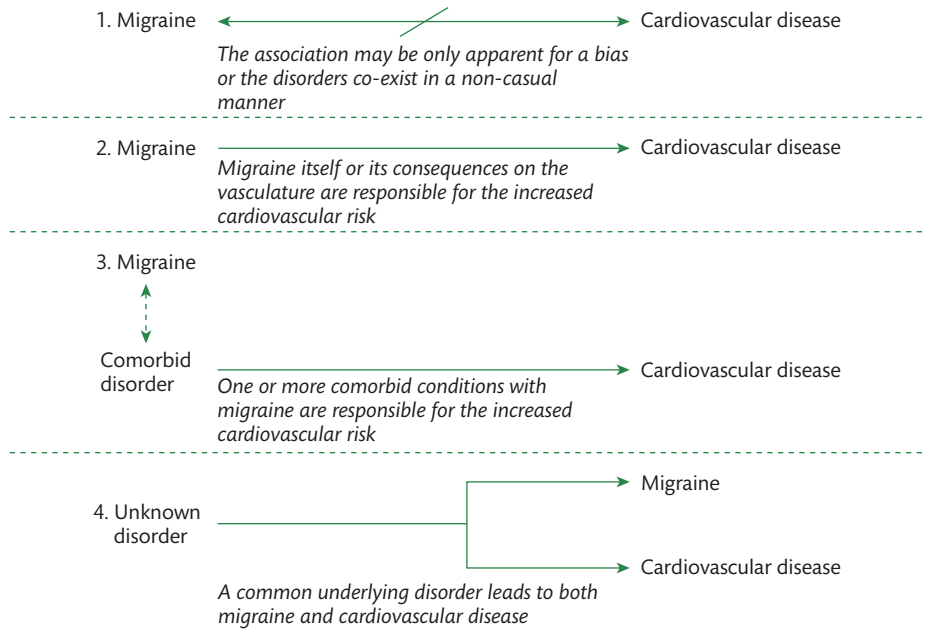
1. Migraine
Cardiovascular disease
The association may be only apparent for a bias or the disorders co-exist in a non-casual manner
2. Migraine
Cardiovascular disease
Migraine itself or its consequences on the vasculature are responsible for the increased cardiovascular risk
3. Migraine
Comorbid disorder
Cardiovascular disease
One or more comorbid conditions with migraine are responsible for the increased cardiovascular risk
4. Unknown disorder
Migraine
Cardiovascular disease
A common underlying disorder leads to both migraine and cardiovascular disease

Figure 10.5 Possible hypotheses to explain the association between migraine and cardiovascular diseases.

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undergoing coronary angiography, those with migraine had less severe coronary artery disease and lower coronary severity scores than those without migraine (78). Moreover, cases of non-atherosclerotic vasospasm of the coronary arteries have been documented in migraineurs with cardiac symptoms (72,79,80).

Migraine has also been associated with an increase in prothrombotic factors, including prothrombin factor, factor V of Leiden, elevations in von Willebrand factor antigen and activity, decreased platelet haemostasis time, clotting time and collagen-induced thrombus formation time, and MTHFR and angiotensin-converting enzyme (ACE) insertion or deletion polymorphisms (81–87). The role of these uncommon vascular risk factors remains to be clarified, even if they can be associated only with a minority of vascular events. Migraine has also been associated with cervical arterial dissection, an acknowledged cause of ischaemic stroke, especially in the young (see also Chapter 37) (88,89). A meta-analysis showed that migraine is associated with a doubling of the risk of cervical artery dissection (88). Although the association was somewhat stronger for MA, there was no significant difference according to aura status (88). Shared genetic susceptibility (90) and increased serum elastase in migraine (91) might be involved. Cervical artery dissection, however, may explain only a minority of the ischaemic strokes occurring in migraineurs.

Attention was given to the involvement of cortical spreading depression (CSD) in the pathogenesis of ischemic stroke in migraineurs (92,93). In CSD the intense neuronal and glial depolarization acts as a potent stimulus to increase regional cerebral blood flow in the cortex (spreading hyperaemia) in order to meet the increased neuronal energy demand. This is followed by more prolonged but moderate hypoperfusion (spreading oligaemia) generally well above the ischaemic threshold (94). A failure of neurovascular coupling to provide a sufficient increase in blood flow for the raised energy use in CSD may lead to neuronal death (95). However, it is more difficult to implicate CSD in vascular events outside the brain (i.e. ischaemic heart disease) and even if it cannot be excluded that other mechanisms may be of importance, it is unlikely that different mechanisms may contribute to the association between migraine and vascular events in and outside the brain. An experimental study suggested that glutamatergic hyperexcitability associated with migraine mutations renders the brain more susceptible to ischaemic depolarizations (96). As a result, the minimum critical level of blood flow required for tissue survival (i.e. viability threshold) is elevated and infarction ensues, even in mildly ischaemic tissues. This represents a paradigm shift in the search for a mechanism for increased stroke risk in migraineurs and differs from those previously postulated on the basis of clinical data alone. The genetic mouse models expressing migraine mutations (e.g. familial hemiplegic migraine and CADASIL) show a faster onset of ischaemia-triggered spreading depolarization; an increased frequency of ischaemic depolarization; enlarged infarcts with worse neurological outcomes (which could be prevented by anti-excitatory treatment); and more severe spreading of depolarization-induced oligaemia (97). As a result, the minimum critical level of blood flow required for tissue survival is elevated and infarction occurs, even in mildly ischaemic tissues. Recently, some authors investigated the hypothesis that history of migraine predisposes to faster acute cerebral infarct growth (98). They performed a case–control study of patients with acute stroke (45 migraineurs and 27 controls), including chart documentation of migraine status and brain MRI within 72 hours of the stroke. In this study, migraine, particularly MA, more frequently showed the no-mismatch pattern with brain diffusion and perfusion MRI. This suggests accelerated loss of viable tissue at risk, as shown in the migraine mouse model (99). In addition, several lines of evidence for vascular dysfunction have been identified in migraineurs and there is increasing evidence to suggest that in migraineurs the vascular system is impaired not only within the brain, but rather in the entire body (100). However,

while several studies support an alteration of arterial function among patients with migraine, findings on the endothelial function are less clear. Endothelial function in migraineurs has occasionally been reported as impaired or altered, while some studies found no difference compared with endothelial function in controls (100). Regarding arterial function, most of the available evidence supports greater stiffness or impaired compliance of the arterial system in migraineurs (100). Possible clinical implications of arterial dysfunction in migraineurs need to be clarified. In the general population, arterial dysfunction has been linked to an increased risk of vascular disease through an atherothrombotic mechanism (101), but, as already reported, migraineurs do not seem to be at increased atherothrombotic risk. Additionally, alteration of circulating factors linked to vascular dysfunction has been found in migraineurs (102–105). Electrophysiological changes could be present not only within the brain, but also in other tissues (e.g. the heart) and a complimentary hypothesis may rely on a systemic peculiar vascular vulnerability of migraineurs that may contribute to the pathogenesis of migraine and over time, to the development of vascular events (106).

Management of the cardiovascular risk of migraineurs

To date, no specific features have been reported that indicate which subjects of the overall migraine population are at the highest risk of vascular events. As stated, the risk of ischaemic stroke in migraineurs is magnified in the presence of some acknowledged vascular risk factors (29,32,35,107,108). In women with migraine, cigarette smoking increases the risk of ischaemic stroke three- to ninefold and oral contraceptive use four- to eightfold (19,20,21,31,32,35). The combination of smoking and oral contraceptive use is associated with a 10-fold increase in risk (31,35). Unfortunately, there are no adequately powered studies to separately determine ischaemic stroke risk for MO and MA patients taking oral contraceptives. Some studies also indicate that arterial hypertension, *MTHFR* gene polymorphisms, and procoagulant states may affect the risk of ischaemic stroke in migraineurs (109). There are, however, no data on vascular risk factors in migraine that are different from those in stroke. Patients with migraine are mostly treated for their pain, but it may be appropriate to manage factors that may increase their basic vascular risk as well (110, 111). Cigarette smoking and arterial hypertension represent well-documented risk factors for cardiovascular disease in the general population and, consequently, basic recommendations about their management should be given to migraineurs The prescription of combined oral contraceptives also deserves special caution (112). As MO is not a definite risk factor for stroke, no specific restrictions are warranted in women with MO, especially in the absence of comorbidities. Oral contraceptives use should, however, be discouraged in women with MA as they have an increased vascular risk. Prescription should be withheld in women with MA, especially when they have comorbid vascular risk factors or congenital or acquired thrombophilia (112).

So far, no drugs are currently recommended for vascular prevention in migraineurs. Indeed, as the risk of developing a stroke in this population is small in terms of absolute numbers, no studies on vascular risk reduction in migraineurs have been conducted (50). It is not known whether treatments used to prevent migraine can also reduce the risk of ischaemic stroke and of other vascular diseases (113,114). If stroke would occur as a consequence of repeated migraine attacks, it could be hypothesized that any treatment able to reduce migraine frequency would be able to reduce the risk of ischaemic stroke. However, drugs that reduce the frequency of migraine attacks would hardly reduce the risk of systemic vascular events. The use of drugs that both treat migraine and prevent stroke should, at least in theory, be more reasonable. To date, however, the available migraine prevention treatments do not show vascular protective effects. ACE inhibitors and angiotensin receptor blockers, which, in preliminary studies, seemed promising in preventing migraine attacks (115,116), were associated with a reduction in the risk of vascular events in normotensive subjects in the presence of benefits beyond those that could be expected only by the reduction of blood pressure values, suggesting the presence of a peculiar effect on arterial or endothelial function (117). However, the effectiveness of these drugs has not been consistently demonstrated for migraine prevention and we do not have any evidence indicating that they may contribute to favourable modulation of the vascular function of migraineurs (118).

Migraine and patent foramen ovale

Initial evidence from case–control studies suggested that migraine and patent foramen ovale (PFO) are associated to an extent that goes beyond what would be predicted by the chance co-occurrence of two common conditions (119–126).

In case–control studies, MA has been found to be associated with PFO in nearly 50% of cases—twice the figure usually reported in non-migraineurs (120–123)—and in patients with PFO migraine has been found twice as frequently as in patients without PFO (124–126). A large population-based study (127) and a hospital-based case–control study (128) questioned the association. Non-blinded and non-randomized studies have suggested benefits of PFO closure on migraine occurrence (129–132). A variable proportion of patients who underwent PFO closure for non-migraine indications reported cessation or improvement of their migraine attacks after the procedure (119). The effect was evident in patients with MO (frequency reduced by 54%) or MA (frequency reduced by 62%) but not for patients with non-migraine headaches (131). However, these studies were limited by being predominantly retrospective, non-randomized, and conducted in highly selected populations of patients. Furthermore, the highly variable course of migraine and the known placebo effects of intervention in previous migraine trials preclude any firm conclusion. The Migraine Intervention With STARFlex Technology (MIST) trial (133), a prospective, randomized, sham procedure controlled trial, was the first randomized controlled study designed to assess the effect of PFO closure on migraine headache in patients with frequent, disabling, and drug-resistant MA (133). In the trial, patients with MA who experienced frequent migraine attacks, had previously failed two or more classes of prophylactic treatments, and had moderate or large right-to-left shunts consistent with the presence of a PFO, were randomized to transcatheter PFO closure with the STARFlex implant or to a sham procedure. No significant difference was observed in the primary end point of migraine

headache cessation between implant and sham groups. Secondary end points also were not achieved. Only in an exploratory analysis, excluding two outliers, did the implant group demonstrate a greater reduction in total migraine headache days. As expected, the implant arm experienced more transient procedural serious adverse events. However, the results of the MIST trial did not allow definite exclusion of any benefit of the PFO closure. In fact, the included patients were selected because they had particularly severe and refractory migraine, which is less amenable to treat than mild or moderate migraine; the continued use of prophylactic migraine medication throughout the trial in both treatment arms may have limited the impact of PFO closure; and the primary study end point of migraine cessation may have been unrealistic and less clinically relevant than reduction in migraine frequency. It should also be tested whether PFO closure may have an impact on aura rather than on pain. Finally, in the MIST trial, the benefits of PFO closure were analysed 3–6 months after device implant. The effect of PFO closure during this relatively early analysis phase may have been confounded by clopidogrel use, incomplete closure of the defect, concomitant pulmonary shunt, and a possible early transient adverse effect of device implant. Therefore, a longer follow-up might have demonstrated additional benefit accrued over time. Residual shunts were assessed by the investigators using contrast transthoracic echocardiography at 6 months. However, it is likely that more residual shunts persisted earlier during the analysis phase, and atrial or pulmonary shunts below the detection threshold of this technique might have had an impact on the treatment effect in this population. Thus, evidence that PFO closure reduce migraine frequency is scarce and this treatment should not be used for the prophylaxis of migraine (134). However, further research on this issue is needed because of the aforementioned limitations of the MIST trial and of experimental evidences that small particles and air bubbles can trigger CSD (135,136), a likely pathophysiological correlate of the migraine aura.

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11

Non-vascular comorbidities and complications

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Migraine comorbidity

Comorbidity was defined in 1970 by Alvan Feinstein as 'any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study' (1). In this definition the term comorbidity could be used for any entity that occurs before the diagnosis, during the disease, or after treatment of the disease. Even 'non-disease' clinical entities such as pregnancy or dieting were included by Feinstein's definition. Nowadays, the term comorbidity is used mostly for associations between disorders that are greater than could be expected based on the usual individual prevalence of both diseases in the given population.

The interpretation of comorbidity between two disorders is not always simple. In fact, (true) comorbidity can be caused by different mechanisms (**Figure 11.1**). The first mechanism is that there is a unidirectional causation, which states simply that migraine may be a risk factor for another disease. In this case, it would be predicted that migraine would occur first. Secondly, when not only migraine increases the risk for a certain disease, but also vice versa (the disease increases the risk for migraine), this is called 'bidirectional comorbidity'. Such a bidirectional relationship is strongly suggestive for shared (environmental and/or genetic) risk factors. In diseases where genetic factors unmistakably play a role, the shared genetic factors hypothesis is particularly attractive (2). Classical twin studies can be used to test whether shared genetic and/or environmental factors underlie the two disorders (3), but direct identification of genetic factors can also be successful when studying cases with both disorders. As a third mechanism of comorbidity, migraine is part of the clinical spectrum of a clear monogenetic disease (i.e. CADASIL, familial advanced sleep phase syndrome (FASPS)).

The number of suggested migraine comorbidities as reported in the scientific literature has increased immensely over the past decades. Research into comorbidity and its underlying mechanisms has become increasingly challenging. Furthermore, migraine patients presenting at a headache clinic or neurology department will often show multiple problems (4). Knowledge about and recognition of this phenomenon has grown among clinicians. Still, the clinical comorbidities create new challenges for patient management, education, and treatment. From a scientific point of view, we note that patient samples are prone to selection (Berkson's) bias, which is the reason why population-based studies are preferable to clinical studies in this instance.

Among the most reported migraine comorbidities, clear associations in population studies have been reported for ischaemic stroke, epilepsy, vertigo, psychiatric diseases, sleep disorders, and pain disorders. Whereas 'migraine, stroke and the heart' (Chapter 10), 'migraine and epilepsy' (Chapter 11) and 'migraine and vertigo' (Chapter 13) are separate chapters in this textbook, we will focus on migraine and psychiatric comorbidity (see also Chapter 52), migraine and sleep disorders (see also Chapter 57), and migraine and pain disorders. Other reported comorbidities often lack convincing evidence because of inconsistent results, study designs with poor statistical power, or highly selected patient populations. Many potential comorbidities have not yet been investigated or have only sparsely been explored. See **Table 11.1** for a list of all clinically relevant investigated comorbidities of migraine and primary references.

Migraine comorbidities have been investigated in both clinical and population-based studies. One of the advantages of clinical studies is that migraine diagnoses are often reliable. One of the main disadvantages is that migraine patients who consult physicians have more frequent and severe attacks than migraineurs in the general population, thereby often overestimating the presence of comorbidities (especially when the comorbidity is associated with migraine severity and frequency). Population-based studies offer a more balanced view on the real extent of the association, although definitions of disease often are less reliable.

Of all studies on comorbidities of migraine most are cross-sectional, complicating the causal interpretation of the results. Only when prospective cohort studies have been done, in which the first onset of disease in a population of migraineurs has been studied, can firm statements on causality be made. The best example in the field of migraine comorbidity is the relationship between migraine and depression. First onset of depression is not only increased in migraineurs, but also first onset migraine is increased in depressive patients. This has led to the recognition of a bidirectional comorbidity, possibly due to shared genetic factors or environmental triggers.

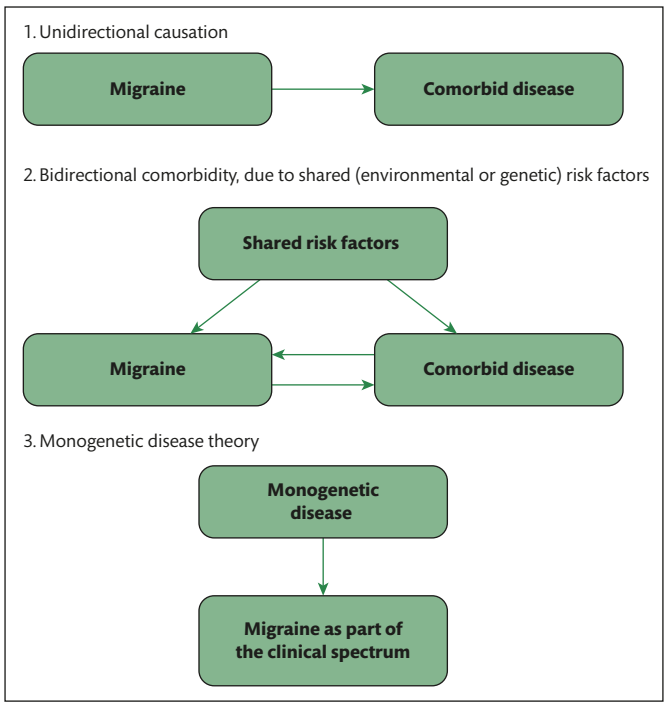

Figure 11.1 Mechanisms of migraine comorbidity.

Migraine and psychiatric comorbidity

The relationship between migraine and psychiatric disorders has been extensively investigated in both population-based and clinical studies (see also Chapter 52). With the development of improved diagnostic criteria and statistical methodology, observations from case series have been confirmed. Multiple studies in particular have focused on the bidirectional association between migraine and depression.

Understanding the associations between migraine and psychiatric disorders is important for various reasons (5). Both migraine and depression are ranked in the top 10 disorders with high disability and burden (6). The presence of psychiatric conditions, especially depression, is a risk factor for migraine chronification (7). In addition, comorbid migraine is associated with poorer functioning and increased somatic complaints in depressed patients (8). Migraine patients with comorbid psychiatric disorders are greater health resources users than migraineurs without psychiatric conditions (9). Lastly, treatment choices for both migraine and psychiatric disorders can be influenced by the presence of comorbidity. Prescription of beta blockers is (although debated) relatively contraindicated as a migraine prophylactic in patients with a comorbid depression. Migraine prophylaxis with selective serotonin re-uptake inhibitors is still controversial because of the suggested risk of developing a serotonin syndrome when prescribed together with triptans, especially when used frequently. However, in our experience this is not a problem in practice. Valproate as prophylactic treatment for migraine may be favoured owing to its stabilizing effect on depressive symptoms.

Depression

Migraine and depression show a bidirectional comorbidity. Population-based studies have shown that persons with a lifetime history of depression have an increased risk of first onset migraine (odds ratio (OR) 3.0, 95% confidence interval (CI) 1.2–7.6) and, vice versa, persons with migraine have an increased risk of first-onset major depression (OR 5.2, 95% CI 2.4–11.3) (10). Such bidirectional association suggests a shared aetiology, which is at least partly explained by genetic factors (11–13). Indeed, evidence suggests that migraine and depression share genetic factors. In a large twin study, 20% of the variability of comorbid migraine and depression was estimated to be due to shared genetic factors and 4% to unique shared environmental factors (14). A study performed in a genetically isolated Dutch population investigated the extent to which the comorbidity of migraine and depression could be explained by shared genetic risk factors. Clear indications were found for shared genetic factors in depression and migraine, especially in migraine with aura (15). Future research should clarify the specific genetic factors that increase liability to both disorders.

The presence of depression is a risk factor for increasing frequency of migraine attacks, thus leading to chronification (6). Treatment of patients with (chronic) migraine and depression is often complicated, because migraine chronification is strongly associated with the overuse of acute headache medication. Medication overuse is present in up to 80% of patients with chronic migraine who are treated in a specialized headache clinic, and in 33% of chronic migraineurs in the general population (6). Depression itself is an important predictor of medication overuse and dependence, and patients with overuse of analgesics are at increased risk of depression (16, 17). Altogether, a triad is suggested of migraine chronification, depression, and medication abuse (Figure 11.2). An important clinical implication of this triad is that patients with chronic migraine should be screened for both medication overuse and comorbid depression. Withdrawal of medication overuse is accepted as a successful treatment for patients with medication overuse headache (18), and could be offered to all patients with chronic migraine and medication overuse.

Beside the general determinants of depression, several migraine-specific determinants involved in this relationship are described. Among others, cutaneous allodynia (the perception of pain in response to non-noxious stimuli to the normal skin) seems to be involved in the relationship between migraine and depression (19,20). Allodynia is considered a clear marker for a central sensitization process of the brain (21). Clinically, central sensitization causes refractoriness to acute treatment. (20). Thus, allodynia has consequences for disease progression and treatment, and it should lead to an increased awareness of comorbidity of migraine and depression, and of risk for chronification of migraine (22).

Anxiety disorders

A strong relationship between migraine and anxiety disorders has been described in the literature, with ORs ranging from 2.7 to 3.2 (23,24). Current anxiety is associated with an increased migraine attack frequency (24). Depression and anxiety are highly comorbid disorders, which could partly explain the relationship between anxiety disorders and migraine. Patients with a combination of anxiety

Table 11.1 Comorbidities of migraine, with key references

Comorbidity	Key references	Type of study	Number of migraineurs	Remarks
Psychiatric disorders				
• Depression	Breslau et al., 2003 (10)	Population based, longitudinal	n = 496	Proves bidirectional comorbidity
• Anxiety	Stam et al., 2010 (15)	Clinic based, cross-sectional	n = 360	Indicates shared genetic factors
• Bipolar disorder	Merikangas et al., 1990 (23)	Population based, longitudinal	n = 61	Distinguishes between depression and anxiety
• Panic disorder	Zwart et al., 2003 (24)	Population based, cross-sectional	n = 6209	–
• Post-traumatic stress disorder	Fornaro and Stubbs, 2015 (28)	Meta-analysis	n = 3976	Primary bipolar cohorts
	Fasmer 2001 (26)	Clinic based, cross-sectional	n = 28	Primary bipolar cohort
	Oedegaard et al., 2010 (27)	Genome-wide association study	n = 56	BPD without headache *vs.* BPD with migraine
	Smitherman et al., 2013 (31)	Review article	–	–
	Stewart et al., 1994 (106)	Population based, cross-sectional	Not provided	Primary panic disorder cohort
	Peterlin et al., 2011 (32)	Review article	–	–
	Peterlin et al., 2011 (107)	Population based, cross-sectional	n = 251	–
Sleep disorders				
• Restless legs syndrome	Rhode et al., 2007 (39)	Clinic based, case–control	n = 411	–
	Chen et al., 2010 (40)	Clinic based, cross-sectional	n = 772	Control groups: TTH and cluster headache
• Narcolepsy	Winter et al., 2013 (44)	Population based, cross-sectional	n = 2816	Self-reported migraine diagnoses
• Insomnia, daytime sleepiness, sleep apnoea	DMKG Study Group 2003 (50)	Clinic based, case–control	n = 21	Primary narcolepsy cohort
	Dahmen et al., 2003 (51)	Clinic based, cross-sectional	n = 37	Primary narcolepsy cohort
	Barbanti et al., 2007 (55)	Clinic based, case–control	n = 100	Outcome measure: excessive daytime sleepiness
• FASPS	Odegård et al., 2010 (56)	Population based, cross-sectional	n = 51	Outcome measure: sleep disturbances
	Lateef et al., 2011 (57)	Population based, cross-sectional	n = 373	Outcome measure: Insomnia
	Kristiansen et al., 2011 (58)	Population based, cross-sectional	n = 109	Outcome measure: sleep apnoea (no association)
	Brennan et al., 2013 (52)	Genetic family study	n = 12	–
Pain disorders				
• Low back pain	Von Korff et al., 2005 (65)	Population based, cross-sectional	Not provided	Primary spinal pain cohort, self-reported migraine
• Fibromyalgia				
• Abdominal pain	Hagen et al., 2006 (66)	Clinic based, cross-sectional	n = 17	Primary low back pain cohort, self-reported migraine
	Le et al., 2011 (67)	Population based, cross-sectional	n = 8044	Self-reported migraine, self-reported comorbidities
	Le et al., 2011 (67)	Population based, cross-sectional	n = 8044	Self-reported migraine, self-reported comorbidities
	de Tomasso, 2012 (68)	Review article	–	–
	Cole et al., 2006 (71)	Health insurance database cohort, cross-sectional	n = 5890	Primary irritable bowel cohort, weak migraine diagnoses
	Kurth et al., 2006 (72)	Clinic based, cross-sectional	n = 99	Outcome measure: upper abdominal symptoms
Gynaecological disorders				
• (Pre-)eclampsia	Facchinetti et al., 2005 (81)	Clinic based, case–control	n = 29	Primary pre-eclampsia cohort
• Endometriosis	Simbar et al., 2010 (82)	Clinic based, case–control	n = 13	Primary pre-eclampsia cohort
• Premenstrual syndrome	Tietjen et al., 2007 (83)	Clinic based, case–control	n = 171	More comorbid conditions in women with endometriosis
	Tietjen et al., 2006 (84)	Clinic based, case–control	n = 50	–
	Karp et al., 2011 (85)	Clinical trial	n = 54	Endometriosis confirmed by biopsy, no association
	Facchinetti et al., 1993 (86)	Clinic based, cross-sectional	n = 34	Association only significant in the menstrual migraine group
	Allais et al., 2012 (87)	Review article	–	–
Movement disorders				
• Parkinson's disease	Barbanti et al., 2000 (108)	Clinic based, cross-sectional	n = 66	Primary Parkinson's cohort
• Essential tremor	Barbanti and Fabbrini, 2002 (109)	Review article	–	–
• Tourette's syndrome	Barbanti et al., 2010 (110)	Clinic based, case–control	n = 28	Primary essential tremor cohort, no association
• Sydenham's chorea	Duval and Norton, 2006 (111)	Clinic based, cross-sectional	n = 30	No association
• Dystonia	Kwak et al., 2003 (112)	Clinic based, cross-sectional	n = 25	Primary Tourette's cohort
	Barabas et al., 1984 (113)	Clinic based, cross-sectional	n = 16	Primary Tourette's cohort, paediatric population
	Teixeira et al., 2005 (114)	Clinic based, cross-sectional	n = 12	Paediatric population
	Barbanti et al., 2005 (115)	Clinic based, cross-sectional	Not provided	Primary dystonia population. No evidence for association

Table 11.1 *Continued*

Comorbidity	Key references	Type of study	Number of migraineurs	Remarks
Other disorders				
• Syncope	Thijs et al., 2006 (74)	Population based, cross-sectional	n = 323	–
• Obesity	Peterlin et al., 2010 (88)	Population based, cross-sectional	n = 4664	Self-reported migraine diagnoses
• Asthma and allergies	Bigal et al., 2007 (89)	Review article	–	–
• Diabetes	Bigal et al., 2006 (90)	Population based, cross-sectional	n = 3791	–
• Multiple sclerosis	Aamodt et al., 2007 (79)	Population based, cross-sectional	n = 5024	–
• Cancer	Burch et al., 2012 (92)	Population based, longitudinal	n = 5062	Self-reported migraine. No evidence for an association
	Rainero et al., 2005 (93)	Clinic based, cross-sectional	n = 30	Outcome measure: insulin sensitivity
	Cavestro et al., 2007 (94)	Clinic based, cross-sectional	n = 84	Outcome measure: glucose metabolism
	Pakpoor et al., 2012 (98)	Meta-analysis	8 studies	Overall OR 2.60 (95% CI 1.12–6.04)
	Kister et al., 2012 (99)	Population based, longitudinal	n = 17,893	Self-reported migraine diagnoses
	Li et al., 2010 (100)	Population based, longitudinal	n = 10,464	Incident breast cancer. Self-reported migraine diagnoses
	Winter et al., 2013 (103)	Population based, longitudinal	n = 7318	Incident breast cancer. Self-reported migraine diagnoses
	Phipps et al., 2012 (105)	Population based, longitudinal	n = 8598	Incident endometrial cancer. Self-reported migraine diagnoses
	Kurth et al., 2015 (104)	Population based, longitudinal	n = 39,534	Incident brain tumours. Self-reported migraine diagnoses

Migraine comorbidities described in literature are summed up with their key references. Comorbidity of migraine with stroke, epilepsy, and vertigo are not mentioned as separate chapters are dedicated to these topics. BPD, bipolar disorder; FASPS, familial advanced sleep phase syndrome; TTH, tension-type headache; OR, odds ratio; CI, confidence interval.

disorders and major depression have been shown to be more likely to have migraine than those with only depression or anxiety (24). The interpretation of the relationship between migraine and depression should therefore always be interpreted in the light of probable comorbid anxiety disorders as the association between migraine and depression seems to be stronger in patients with co-existing anxiety disorders (23–25).

Bipolar disorder

A few studies have investigated the relationship between migraine and bipolar mood disorders. In a prospective cohort study among 27- and 28-year-olds in Zurich, Switzerland, the 1-year prevalence of a bipolar spectrum disorder was 8.8% in migraineurs versus 3.3% in non-migraineurs (OR 2.9, 95% CI 1.1–8.6) (23). In a psychiatric inpatient population, migraine appeared to be most prevalent in patients with a bipolar II disorder (77%), when compared with unipolar depressive disorder (46%) and the bipolar I disorder (14%) groups (26).

A genome-wide association study was performed in a sample of patients with bipolar affective disorder (using comorbid migraine as an alternative phenotype). A single nucleotide polymorphism was suggested to be associated with bipolar disorder and attention-deficit–hyperactivity disorder in patients with migraine. However, this finding was never replicated by others (27).

A recent systematic review and meta-analysis established that, overall, approximately one-third of people with bipolar disorder are affected by comorbid migraine (28,29). The finding that migraine is more prevalent among people with bipolar II disorder than in those with bipolar I disorder was confirmed in this studies.

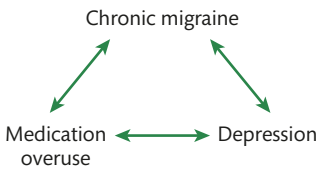

Figure 11.2 Triad of migraine chronification.

Other psychiatric comorbidities

Relationships have been described of migraine with panic disorder, obsessive–compulsive disorder, phobias, and post-traumatic stress disorder (23,25,30–32). Only cross-sectional studies were performed, complicating the causal interpretation of these relationships. Further research is needed to enlighten the interaction of different psychiatric disorders and their comorbidity with migraine. The exact mechanisms underlying most of the psychiatric comorbidities of migraine are poorly understood, with the clear exception of depression for which more clues are provided for shared (genetic) risk factors.

Migraine and sleep disorders

Sleep disorders have been reported to occur more often in migraineurs than in persons without migraine (see also Chapter 57). Among sleep disorders associated with migraine are restless legs syndrome (RLS), narcolepsy, insomnia, and obstructive sleep apnoea (OSAS) (33). Migraine is associated with sleep in different ways: patients often report their migraine attacks to start during nocturnal or diurnal sleep, on the one hand. On the other hand, many patients report sleep as an important factor of relief for their migraine attacks. These findings indicate that the physiology of sleep could somehow be related to the mechanisms underlying migraine attacks (34). The frequent association of headache (in general) and sleep might be defined by different paradigms: firstly, headache as a result of disrupted nocturnal sleep (i.e. OSAS or RLS). Secondly, headache might be the cause of sleep disturbances (i.e. chronic tension-type headache or chronic migraine, and also cluster headache). Lastly, there could be an intrinsic (anatomical and/or physiological) relationship between the headache disorder and sleep, as being suggested for migraine, cluster headache, and hypnic headache (34).

The relationship between migraine and sleep, with the occurrence of migraine often during nocturnal sleep and awakening, as well as the periodic nature of migraine and the premonitory symptoms occurring in migraine, suggest that migraine may be associated with the chronobiology. Also, reported triggers such as hormonal changes (menstruation), jet lag, shift work, seasonal cycles, and work–rest activity (weekends) support the theory that chronobiology plays an important role in migraine pathophysiology. The chronobiology is regulated by the hypothalamus, suggesting involvement of the hypothalamus in the pathophysiology of migraine (35). Consequently, associations between migraine and sleep disorders are suggestive of hypothalamic modulation of the trigeminovascular pathway (34,35). Pain signals that originate in the trigeminovascular pathway can alter the activity of hypothalamic and limbic structures that integrate sensory, physiological, and cognitive signals that drive behavioural, affective, and autonomic responses (36).

Restless legs syndrome

RLS is characterized by an urge to move, mostly associated with unpleasant leg sensations, occurring at rest, in a circadian pattern, diminishing with motor activity (37). RLS hampers sleep and has a negative impact on quality of life (38). Several epidemiological studies have provided evidence for a bidirectional association between migraine and RLS in clinical cohorts (39,40). RLS prevalence rates in migraine populations are about twice as high as prevalence rates in the general Western population: 11–18% in migraine populations versus 5–10% in general populations (39–45). RLS is, according to a recent cross-sectional study, not only twice as prevalent, but also more severe in migraine patients, and associated with decreased sleep quality (46).

RLS has long since been considered to be related to dopaminergic system dysfunction (47,48). Dopaminergic dysfunction has also been linked to the pathogenesis of migraine, especially to clinical premonitory symptoms such as nausea, vomiting, hypotension, and drowsiness (49). Another possible link between migraine and RLS could be that sleep deprivation in patients with RLS triggers migraine attacks. Co-associations are found with depression, which could also influence this comorbidity (39).

Narcolepsy

Narcolepsy is a disorder of the sleep–wake cycle with a prevalence of approximately 20–60 per 100,000 (50). Only a few studies have been published on the comorbidity of migraine and narcolepsy. The main symptoms are excessive daytime somnolence, cataplexy, hypnagogic hallucinations, sleep paralysis, disturbed nocturnal sleep, and cataplexy (51). All studies on the comorbidity of migraine with narcolepsy have been performed in clinical narcolepsy populations, most probably due to the low prevalence of narcolepsy. Conflicting results have been reported: some report a clear significant association with migraine in a cohort of narcoleptic patients (51), and others report no association with migraine, but only with the occurrence of 'unspecific headache' (50). More investigations are needed to explore the relationship between migraine and narcolepsy.

Familial advanced sleep phase syndrome

Two families were identified with both familial migraine with aura and FASPS, which appeared to be inherited in an autosomal dominant manner (52). This syndrome is defined by a profound phase shift of the sleep–wake cycle. A mutation was identified from this family in the casein kinase 1δ gene, being involved in the circadian clock regulation. Testing in transgenic mouse models suggested an increased cortical excitability, consistent with a susceptibility to migraine with aura (53). These findings suggest that circadian dysregulation may be common to migraine in general (54). This type of comorbidity, however, in which a single gene seems to increase the sensitivity for both migraine and another disease, is both exceptional and unique.

Insomnia, daytime sleepiness, and sleep apnoea

Associations of headache with sleep disturbances in general, including excessive daytime sleepiness, insomnia, snoring, and/or apnoea, have been investigated thoroughly by several studies. However, few of those studies have focused particularly on migraine. Sleepiness is considered a possible migraine symptom that can emerge during various phases of a migraine attack, including the premonitory phase, the headache phase and the recovery phase. A case–control study of 100 patients with episodic migraine and 100 healthy controls indicated that daytime sleepiness was more frequently present in migraineurs than in controls (OR 3.1, 95% CI 1.1–8.9) (55). One population-based study evaluated sleep disturbances in 297 participants, of whom 51 were diagnosed with migraine. Compared with migraine-free controls, patients with migraine had significantly more severe sleep disturbances (OR 5.4, 95% CI 2.0–15.5), with a stronger association for chronic headache patients (56). Another population-based study including 373 migraineurs indicated that migraineurs versus healthy controls had more difficulty in initiating sleep (OR 2.2, 95% CI 1.6–3.0), difficulty in staying asleep (OR 2.8, 95% CI 2.3–3.5), more early morning awakening (OR 2.0, 95% CI 1.4–2.7), and more daytime fatigue (OR 2.6, 95% CI 2.0–3.3) (57). However, no differences between migraine and other types of headache were found, nor were there differences between migraineurs with and without aura. No relationship between migraine and sleep apnoea was found in a cross-sectional population-based study (58).

Migraine and pain disorders

Several (chronic) pain syndromes have been described to be comorbid with migraine, including low back pain, fibromyalgia, and irritable bowel syndrome (IBS). The fact that many persons with migraine suffer from other pain conditions is suggestive of (subtle) changes in the function of the nociceptive system (20). However, willingness to report pain may also play a role. Repeated or prolonged noxious stimulation may lead to sensitization, a phenomenon defined by increased neuronal responsiveness within the central nervous system (59). In migraine, the clinical marker for central sensitization is considered to be cutaneous allodynia (the perception of pain in response to non-noxious stimuli to the normal skin). Migraine patients experience an increased sensitivity to the skin for common daily common daily activities during migraine attacks, such as combing of hair, taking a shower, touching the periorbital skin, shaving, or wearing earrings during migraine attacks (60). Prevalence estimates of allodynia in migraine patients range from 50% to 80% (61). Factors that have been reported to increase the likelihood of having allodynia during migraine attacks are female sex, high body mass index, and headache-specific features such as a low age at onset, high frequency of attacks, and comorbidity with

depression and anxiety (19,20,60,62–64). Allodynia also has been described as a predictor for migraine chronification (22).

In a large clinic-based migraine study, several comorbid chronic pain conditions were associated with migraine-related cutaneous allodynia (20). These findings support the theory that the presence of allodynia in migraine patients marks an increased risk for other diseases that have been associated with central sensitization. A shared pathophysiological link between migraine and other pain syndromes might be sensitization of central pain pathways. Longitudinal studies are needed to evaluate the temporal relationship of chronic pain conditions and migraine.

Low back pain

Chronic low back pain is typically comorbid with a range of other chronic pain conditions. In a large cross-sectional population-based survey, an association was found with migraine (OR 5.0, 95% CI 4.1–6.4) (65). However, migraine diagnoses were self-reported, and chronic back pain was defined as self-reported 'chronic back or neck problems'. A smaller association was found in a clinical population of patients with chronic low back pain (OR 1.6, 95% CI 1.1–2.3) (66). However, this study had similar drawbacks, with migraine diagnoses not fulfilling International Classification of Headache Disorders, second edition (ICHD-2) criteria. Another population-based study found that low back pain was highly prevalent in migraine patients (OR 1.77, 95% CI 1.62–1.94) (67). Altogether, associations between chronic low back pain and migraine have been described, but the magnitude and background of this comorbidity remain unclear.

Fibromyalgia

Fibromyalgia is a chronic pain syndrome of unknown aetiology characterized by diffuse pain and the presence of so-called 'tenderness points'(see also Chapter 58). The most supported hypothesis on the causes of fibromyalgia is that central sensitization might cause musculoskeletal pain (68). A review study of comorbidity with primary headache syndromes found seven papers investigating the relationship of fibromyalgia with migraine. The prevalence of fibromyalgia appears to be increased in migraine patients (ranging from 10% to 36% versus 3–6% in the general population). Furthermore, chronic headache types show higher prevalence rates than episodic headache types (68). A large Danish migraine comorbidity study presented an increased comorbidity for migraine with aura (OR 6.63, 95% CI 3.74–11.76) when compared with migraine without aura (OR 2.04, OR 1.01–4.13) (67). Patients with migraine and co-existing fibromyalgia have a higher risk of suicidal ideation and suicide attempts compared with migraine patients without fibromyalgia (69). The association is stronger with increasing migraine attack frequency and migraine burden. This finding suggests that patients with migraine should be carefully evaluated for other chronic pain conditions and for their mental health well-being (70).

Abdominal pain

IBS is a functional disorder of the gastrointestinal tract, which results in the clinical symptoms of altered bowel habits and abdominal pain (71). People with IBS are reportedly more likely to have other disorders, including migraine. A health insurance database study of 97,593 patients with a medical claim for IBS showed an increased comorbidity of migraine within this population (OR 1.6, 95% CI 1.4–1.7) (71). However, a major drawback of studies of these kind of databases is that prevalence numbers are not reliable. A clinical study of 99 migraineurs showed (in comparison with a population of 488 blood donor controls) an increased prevalence of upper abdominal pain, frequent abdominal pain, abdominal pain (in general), night abdominal pain, and periodic abdominal pain (all *P*-values <0.001) (72). Remarkably, the relationship of abdominal complaints and migraine has also been attributed to 'adult abdominal migraine' in a case report (73). Abdominal migraine, according to the ICHD-2 criteria, typically occurs during childhood. It remains unclear whether abdominal complaints during attacks in migraine patients can be classified as abdominal migraine, but usually these complaints involve not so much as pain, as well as nausea, vomiting, and diarrhoea.

Migraine and other comorbidities

Syncope

Syncope is a paroxysmal symptom consisting of a brief, self-limiting transient loss of consciousness due to global cerebral hypoperfusion (74). Syncope is associated with dysfunction of the autonomic nerve system, which also has been studied in migraineurs (with conflicting results). Only one large population-based study investigated both the prevalence of syncope and related symptoms of the autonomic nerve system (74). The prevalence of one or more syncopal events in 323 migraineurs versus 153 controls was higher in migraineurs, both for syncope (46% vs 31%; $P = 0.001$) and frequent syncope (13% vs 5%; $P = 0.02$). There was no significant difference between the migraine and control groups in measurements of autonomic dysfunction. The reason for this association is presently uncertain. The Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis (CAMERA) study shows that frequent syncope, orthostatic intolerance, and migraine independently increase the risk of white matter lesions, particularly in females (75).

Two families were reported with migraine and syncope (76,77). This could be an indication that there could be a genetic predisposition for the comorbidity of migraine and syncope. However, additional studies are required to investigate the probable genetic background of this comorbidity.

Movement disorders

Associations with migraine have been reported for Parkinson's disease, essential tremor, Tourette's syndrome, Sydenham's chorea, and dystonia (78). The pathophysiological explanation for these comorbidities has been described as involvement of the basal ganglia in both movement disorders and migraine. To date, however, it is still unclear to what extent the basal ganglia indeed are involved in migraine.

Asthma and allergies

A large population-based study from Norway investigated the relationship between migraine (and non-migrainous headache) and asthma, hay fever, and chronic bronchitis. This study showed that migraine was associated with current asthma (OR 1.5, 95% CI 1.3–1.7), hay fever (OR 1.5, 95% CI 1.4–1.6) and chronic bronchitis (OR 1.6, 95% CI 1.3–1.8) (79). The pathophysiological explanation for these associations is suggested to be that mast cells (which are evidently

involved in asthma pathogenesis) could also play a role in migraine genesis as well by secretion of vasoactive, pro-inflammatory, and neurosensitizing mediators (80).

Gynaecological comorbidities

Several gynaecological disturbances have been associated with migraine. Endometriosis (which also could be considered a chronic pain syndrome), menorrhagia, (pre-) eclampsia, and the premenstrual syndrome all have been reported as being associated with migraine (81–87). However, the scientific strength of these relationships is mostly moderate, with only few reports. Whether central sensitization (in case of endometriosis) the female sex hormones, or altered platelet function play a role in this suggested comorbidity, is to be clarified by future research.

Obesity

The relationship of migraine with obesity has been studied in several large population-based studies (88–90). Interestingly, in one study, the association of migraine with obesity was only significant in younger migraine patients (<56 years) (88). These findings support not only the association between migraine prevalence and obesity, but also the theory that adipose tissue disposition plays a role in this comorbidity. A systematic review and meta-analysis of observational studies confirms the association between migraine and obesity, likely mediated by sex, migraine frequency, and age (91).

Diabetes

Insulin resistance as a component of metabolic syndrome has been proposed as being a part of the associations between migraine, obesity, and increased cardiovascular disease risk. The Women's Health Study, a large prospective cohort study of women aged >44 years, investigated the association between migraine status and incident type 2 diabetes (92). No associations were found. Others, however, describe alterations in insulin metabolism in migraineurs, albeit without defining diabetes (93,94). The other way around, in persons treated for diabetes, a reduced prevalence of migraine medication intake was found, suggesting a reduced migraine prevalence of migraine among (older) patients with diabetes (95). It is plausible that these inconsistent results may be due, in part, to the age of the studied populations. For example, selective mortality, diabetic neuropathy, or vascular changes suppressing the expression of migraine in later life might lead to a different association between migraine and diabetes in younger versus older adults. Consistent with this hypothesis is the previously referenced study showing a different relationship between obesity and migraine in younger versus older adults (88). Notably, a longitudinal study from Norway found increased incidence of metabolic syndrome in migraineurs compared with others over 11 years of follow-up (96,97). In conclusion, the exact relationship between migraine and diabetes is still very unclear. The question of whether diabetes is independently associated with migraine, or just as a confounder in the association between migraine and cardiovascular disease, should be studied in longitudinal study designs.

Multiple sclerosis

The proposed relationship between migraine and multiple sclerosis (MS) has been investigated in several studies. A recent meta-analysis of studies on this relationship provided an overall estimate by comparing the occurrence of migraine in patients with MS versus controls, showing a significant association, with patients with MS being twice as likely to report migraine as controls (OR 2.60, 95% CI 1.12–6.04) (98). A large prospective cohort study among nurses (the Nurses' Health Study II) calculated the relative risk of MS as being 1.39 (95% CI 1.10–1.77) in study participants with versus without migraine (99). Altogether, a clear association between migraine and MS has been proven. Various hypotheses have been proposed that may explain this association, including misdiagnosis of MS (due to non-specific radiographic findings in combination with a history of transient neurologic deficits), migraine-like headache as a presenting symptom of MS, and changes in the physiology of the migraine brain facilitating the pathogenesis of MS (99).

Cancer

Few studies have been performed on the relationship between migraine and cancer, all of which focused on 'female cancers': breast cancer and endometrial cancer. As a reason for this specific focus, most papers put forward that migraine predominantly affects women, with a reported role of hormonal fluctuations in a part of these patients. Interestingly, two case–control studies and one prospective study suggested that a history of migraine is associated with a reduction in the risk for breast cancer (10–30% reduction) (100–102). However, the Women's Health Study showed in a prospective design no significant association of migraine with breast cancer risk (HR 1.10, 95% CI 0.99–1.22), nor with the occurrence of brain tumours (HR 1.18, 95% CI 0.58–2.41) (103,104). A study on the risk of postmenopausal endometrial cancer in women with a migraine history showed no association (HR 0.91, 95% CI 0.75–1.11) (105). Altogether, the relationship between migraine and cancer is far from evident.

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12

Migraine and epilepsy

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General concepts

Migraine and epilepsy are both characterized by transient attacks of altered brain function with a clinical, pathophysiological and therapeutic overlap (1–10). Furthermore, epilepsy and migraine may mimic each other. In particular, occipital lobe seizures may be easily misinterpreted as migraine with visual aura (11)—although there seem to be several clinical characteristics that can differentiate between visual auras of epileptic and migrainous origin (12).

The frequency of epilepsy in people with migraine (range 1–17%) is higher than in the general population (0.5–1%), just as the prevalence of migraine among patients with epilepsy is also higher than that reported in healthy individuals (3,13–18). This comorbidity is often found especially in children (19,20). Some studies of the association between migraine and specific epilepsy syndromes, such as childhood epilepsy with occipital paroxysms and benign childhood epilepsy with centrotemporal spikes, were negative (6,21), but others were positive (3,22–27).

An increase in (usually unspecific) electroencephalographic (EEG) abnormalities in patients suffering from migraine (9) has been considered as further evidence of a relationship between migraine and epilepsy (11,13). The mechanism underlying the onset of a migraine attack is probably cortical spreading depression (CSD). Unlike epileptiform abnormalities in epilepsy attacks, CSD is not demonstrable in the EEG of migraine patients, which clearly hampers studies addressing the pathophysiological overlap between migraine and epilepsy attacks.

Pathophysiology

Seizures and migraine attacks share several pathophysiological mechanisms (28). Both phenomena may be symptoms of an underlying brain lesion, or have a genetic origin. Lesions in the occipital lobe may be associated with migraine and occipital lobe epilepsy (6). Both occipital epilepsy and migraine are characterized by visual symptoms (elementary visual hallucinations vs aura) followed by headache and other autonomic symptoms.

Epileptic seizure–migraine attack: common substrates

Many studies support the hypothesis of excessive neocortical cellular excitability as the main pathological mechanism underlying the onset of attacks in both diseases (2). In migraine, however, hyperexcitability is believed to result in CSD rather than in the hypersynchronous activity that characterizes a seizure. Moreover, in migraine hypo- and hyperexcitation occur sequentially as rebound phenomena (during a spreading depression); hence, the term 'dis-excitability' may better describe migraine pathophysiology than hyperexcitability (29). CSD could be a connecting point between migraine and epilepsy (30–33). CSD is characterized by a slowly propagating wave of sustained strong neuronal depolarization that generates transient intense spike activity as it progresses into the brain tissue, followed by neural suppression, which may last for minutes. The depolarization phase is associated with an increase in regional cerebral blood flow, whereas the phase of reduced neural activity is associated with a reduction in blood flow (34). CSD causes activation of the trigeminovascular system (TVS), consisting of the cascade release of numerous inflammatory molecules and neurotransmitters, which results in pain during the migraine attack (35).

In both CSD and a seizure, the onset and propagation of neuronal depolarization are triggered when a certain threshold is reached, which is supposed to be lower for CSD than for a seizure (36–40).

Once the cortical event has started, spreading subsequently depends on the size of the onset zone, velocity, semiology, and type of propagation. Moreover, the onset of CSD and that of the epileptic seizure may *facilitate* each other (29,41). These two phenomena may be triggered by more than one pathway converging upon the same destination: depolarization and hypersynchronization (29,32,33,41,42). A paroxysmal change in cortical neuronal activity may occur during a migraine attack or epilepsy seizure; hyperexcitation occurs in epilepsy, whereas in migraine hypo- and hyperexcitation occur sequentially as rebound phenomena (spreading depression) (43,44). The triggering causes may be environmental or individual (genetically determined or not), which result in a flow of ions that mediates CSD, through neuronal and glial cytoplasmic bridges rather than through interstitial spaces, as usually occurs in the spreading of epileptic seizures (29,41,42). The

threshold required for the onset of CSD is likely to be lower than that required for the epileptic seizure. In this regard, a 'migraleptic' event (see section 'Migraine-triggered seizure (migralepsy) and ictal epileptic headache') would be unlikely to occur. Recurrent seizures might also predispose patients to CSD, thereby increasing the occurrence of a peri-ictal migraine-type headache, usually a post-ictal headache (29,33,41,45). However, in chronic epilepsy, an intrinsic protection mechanism against CSD may exist, as was suggested by the strongly increased threshold for CSD in brain slices from patients suffering from chronic epilepsy (46).

Epileptic syndromes–primary headache/migraine: common substrates

In specific childhood epilepsy syndromes migraine/headaches seem more prevalent (6,23,26,47,48). The best known are benign occipital epilepsy of childhood with occipital paroxysms (BOEP) and benign rolandic epilepsy. The seizures in BOEP usually begin with visual symptoms, including amaurosis, elementary visual hallucinations (phosphenes), and complex visual hallucinations (visual illusions) (47), followed by hemiclonic, complex partial, or generalized tonic-clonic seizures. Approximately 25–40% of these patients develop migraine- like headaches (6). Therefore, occipital seizures may be erroneously diagnosed as migralepsy (47,49).

Both migraine and epilepsy have an important genetic component. The rare monogenic forms of migraine are of the familial hemiplegic migraine (FHM) subtype (50). Strong support for a shared genetic basis between headache and epilepsy comes from clinical/EEG and genetic studies on FHM (51–60)—errors in the same gene may be associated with migraine in some cases and with epilepsy in others (53). Recent data suggest shared genetic substrates and phenotypic–genotypic correlations with mutations in some ion transporters genes, including *CACNA1A, ATP1A2*, and *SCN1A* (54–59). Several other genetic findings pointing to a link between migraine and epilepsy have been reported. They include mutations in SLC1A3, a member of the solute carrier family that encodes excitatory amino acid transporter 1, 57 POLG58, C10, and F259, which encode mitochondrial DNA polymerase and helicase twinkle (59,60).

Although much remains to be understood of the pathophysiology of epilepsy and migraine, glutamate metabolism (61), serotonin metabolism (62), dopamine metabolism (63), and ion-channel function (sodium, potassium, and chloride) might be impaired in both (64). In particular, it is likely that voltage-gated ion channels are critically positioned in the pathways associated with migraine and epilepsy (54–60).

Photosensitivity

Intermittent photic stimulation (IPS), may induce photoparoxysmal EEG responses (PPRs), migraine, and epileptic seizures (45). Some patients with ictal epileptic headache (IEH) (21,65) were photosensitive (21,66–69). Although occipital lobe epilepsy already has much in common with migraine (visual aura; positive and negative ictal signs; and autonomic disturbances, such as pallor and vomiting), the photosensitive variant of occipital epilepsy and photosensitive epilepsy, in general, share even more similarities, such as a higher prevalence in women (female to male ratio of 3:2) and a sensitivity to flickering light stimuli and striped patterns with provocation of attacks (45).

In children affected by migraine with aura (MA), a PPR was seen in over one-third (70), which is more than reported in a healthy population of children (1.4%) and in epilepsy patients in general (5%) (71). In another study that investigated the PPR frequency and type in 263 children and adolescents between 7 and 18 years of age affected by primary headache, Wendorff et al. (72) found that the PPR frequency did not differ significantly in the three main types of headaches, ranging from 6.7% (tension-type headache) to 8.9% (migraine without aura (MO)). However, PPR was most frequent (17.6%) in the MA group of patients under 12 years of age, and in seven of 17 patients with both migraine and PPR, photogenic stimuli were the most frequent triggering factors of the migraine attack, compared with 10 of 100 controls (<0.01) (45).

Propagation of PPR is associated with increased excitability of the occipital cortex (73). In this regard, it should be borne in mind that the accumulated burden of migraine seems to cause slight alterations in the physiology of the visual cortex and an increase in alpha rhythm variability up to 72 hours before the next migraine attack (74). Flashes, phosphenes, and other positive or negative visual manifestations are often part of the clinical picture in migraine and occipital epilepsy (75). Moreover, IPS induces 'flashes and phosphenes', as well as migraine and seizures.

Finally, photophobia is one of the most well-known features of migraine (80% of chronic migraineurs (76)) and also often found in epilepsy-related headaches (in 50% of cases it occurs in pre-ictal, postictal, or even interictal headache (77)).

In summary, a subclinical spontaneous (epileptic foci or CSD) (41,78,79) or induced (IPS or other visual stimulations) (64,79) cortical event might, depending on the cortical or subcortical neural network threshold and on the speed and direction of propagation, result in a seizure, in migraine or in both. In exceptional cases (IEH), which occur almost exclusively in childhood, the subclinical focus might consist of an epileptic focus that activates the TVS, thereby inducing migraine without any other known cortical epileptic signs or symptoms (41,45,78,80).

Drug treatment

The hypothesis that migraine may be related to neurotransmitter or ion-channel dysfunctions makes it interesting to analyse the effect of antiepileptic drugs (AEDs) on migraines. Several authors have demonstrated the effectiveness of AEDs (i.e. valproate, topiramate) in preventing migraine attacks (81–83). AEDs reduce neuronal hyperexcitability by various mechanisms (84). Consequently, these results are consistent with the concept that hyperexcitability is responsible for triggering aura and the subsequent headache. However, other AEDs, including phenytoin, oxcarbazepine, vigabatrin, and clonazepam, are not effective in migraine prophylaxis (9). It is possible that AEDs that act primarily via use-dependent blocking of voltage-gated sodium channels, or that act via γ-aminobutyric acidergic (GABAergic) mechanisms, appear to influence mechanisms that are not relevant to migraine (85).

The use of AEDs for migraine may also elucidate differences between epilepsy and migraine patients, warranting further studies. Firstly, migraine patients seldom experience remission from attacks when using these drugs, whereas in epilepsy the majority of patients will achieve remission on any AED. Furthermore, migraine patients

tolerate AEDs less well. Luykx et al. systematically compared the profile and frequency of adverse reactions to topiramate as reported in six migraine and four epilepsy randomized controlled trials (86). They found both qualitative and quantitative differences between the two patient populations. Migraineurs were more likely to drop out because of topiramate-related adverse responses, particularly in the 50 mg group, confirming the clinical impression that migraineurs are at higher risk of (unacceptable) adverse drug reactions than epilepsy patients.

Classification issues

Peri-ictal and interictal headache

Seizures and epilepsy syndromes are usually classified according to the guidelines of the International League Against Epilepsy (ILAE) (87), and headaches according to the International Classification of Headache Disorders (ICHD). The current version, the ICHD-3, was published in 2018 (88).

Seizure-related headaches (SRHAs) can be divided into peri-ictal (peri-IHA) and interictal headache (inter-IHA). peri-IHA can be divided into pre-ictal (PIHA), ictal (IHA) and postictal headache (post-IHA). PIHA headaches occur in 5–15% of cases, IHA in 3–5%, post-IHA in 10–50% of cases, and inter-IHA in 25–60% (89,90). A recent study showed that only one-quarter of peri-IHA episodes can be classified according to the ICHD-3 criteria (91). The fact that there is still no consensus on the classification of epilepsy-related headaches emphasizes the need to get together experts from both the ILAE and the International Headache Society to come to such a consensus (92).

To date, only three specific entities of seizure-related headaches are considered in the ICHD-3 classifications (**Box 12.1**): hemicrania epileptica (7.6.1), post-HA (7.6.2), and migraine-triggered seizure (migralepsy) (1.5.5). Diagnostic criteria for the new entity 'ictal epileptic headache' (IEH) (**Box 12.1**) have recently been proposed (90).

Hemicrania epileptica/ictal headache

Hemicrania epileptica/ictal headache is recognized as an ipsilateral headache with migraine-like features occurring as an ictal manifestation of the seizure discharge. Diagnosis requires the simultaneous onset of headache with epileptiform EEG abnormalities (11).

In published cases, the duration of the ictal headache justified their classification as non-convulsive status epilepticus (SE) (21,45,65,78). Four patients showed occipital partial SE in the EEG (30,66–69), while bilateral continuous spike-and slow-wave discharges (i.e. absence status) were reported in one case (67). Headache could be ipsi- or contralateral to the ictal epileptiform discharge (21,65–69).

Postictal headache

Post-IHA is the most frequent headache type associated with seizures (93). It is defined as a headache with features of tension-type headache or of migraine, which develops within 3 hours of a generalized or partial seizure, and resolves within 72 hours after the seizure (**Box 12.1**). Although it is common, occurring in about 50% of epileptic patients, it is often neglected because of the dramatic impact of the preceding seizure. Post-IHA has been reported in patients with symptomatic epilepsy, but it is especially frequent in idiopathic occipital seizures (25). It has been suggested that the seizure discharges in the occipital lobes trigger a genuine migraine through CSD and activation of trigeminovascular or brainstem mechanisms (5,6).

Interictal headache

Inter-IHA is a headache not temporally related to a seizure. Verrotti et al. (18) analysed the prevalence of peri-IHA and inter-IHA and clinical characteristics and their temporal correlations with seizure onset in a large sample of newly diagnosed children and adolescents with idiopathic epilepsy. Post-IHAs and inter-IHAs were the most frequent (62% and 58%, respectively), as in adult studies, while PIHAs were found in only 30% (14,18,94–96). Regarding the burden of SRHA, paediatric studies showed that peri-IHAs were often severe and long-lasting, especially in post-IHA.

Migraine-triggered seizure (migralepsy) and ictal epileptic headache

According to ICHD-2, migralepsy is a recognized complication of migraine (Table 1). Migralepsy does not exist in the classifications of ILAE. The term 'migralepsy' is old, deriving from migra(ine) and (epi)lepsy, used for the first time by Lennox and Lennox in 1960 (although they attributed it to Dr Douglas Davison), to describe a condition wherein 'ophthalmic migraine with perhaps nausea and vomiting was followed by symptoms characteristic of epilepsy' (9). However, most reported cases of 'migralepsy' do not allow the dissection of a meaningful and unequivocal migraine–epilepsy sequence (21,64).

There are at least 50 potential cases of migralepsy reported in the literature (1–3,6,97–107), the majority of which have been the subject of criticism by several authors (11,78,97,106–108). In fact, the diagnosis in the majority of these cases is uncertain because the information available is not clear (38%), the cases do not fulfil the current ICHD-3 criteria (30%), or the diagnosis is questionable (28%) (98). Indeed, most of the previous reports of 'migralepsy' may have been occipital seizures imitating MA (4,6,7,107–112).

Although unequivocal epileptiform abnormalities in patients with paroxysmal sensations or behavioural changes usually point to a diagnosis of epilepsy, the lack of clear ictal epileptic spike-wave activity is frequent in autonomic epilepsies, such as Panayiotopoulos syndrome (30,45). In such cases, ictal epileptic EEG activity might be recorded as unspecific slow-wave abnormalities without any spike activity. Interestingly, there may, on rare occasions (2), be an isolated epileptic headache that has no associated ictal epileptic manifestations or scalp EEG abnormalities but whose ictal epileptic origin can be demonstrated by depth electrode studies (2). The epileptic focus that activates the TVS might thus remain purely autonomic (it being associated exclusively with migraine complaints), without ictal neuronal activation of non-autonomic cortical areas (different neuronal network thresholds appear to be involved); in this case, the focus fails to reach the symptomatogenic threshold required to induce sensory–motor manifestations, as has been described for other ictal autonomic manifestations in Panayiotopoulos syndrome (41,113).

IEH can be considered an autonomic form of epilepsy, like Panayiotopoulos syndrome (114). Accordingly, cases with long-lasting IEH episodes fulfil the criteria to be considered as 'autonomic status epilepticus' (115).

Since 1983, 12 cases of IEH according to proposed criteria (Table 1) (35) have been reported (2,21,64,66,68,97,116,117). Parisi et al.

Box 12.1 Classification of headache-related seizures (ICHD-3) and the original proposed criteria for ictal epileptic headache

1.4.4 Migraine aura-triggered seizure

Diagnostic criteria:

A A seizure fulfilling diagnostic criteria for one type of epileptic attack, and criterion B below.

B Occurring in a patient with '1.2 Migraine with aura', and during or within 1 hour after an attack of migraine with aura.

C Not better accounted for by another ICHD-3 diagnosis.

7.6 Headache attributed to epileptic seizure

Coded elsewhere:

Where migraine-like or other headache and epilepsy are both part of a specific brain disorder (e.g. MELAS), the headache is coded to that disorder. Where a seizure occurs during or immediately following a migraine aura, it is coded as '1.4.4 Migraine aura-triggered seizure'.

Description:

Headache caused by an epileptic seizure, occurring during and/or after the seizure and remitting spontaneously within hours or up to 3 days.

Diagnostic criteria:

A Any headache fulfilling criterion C.

B The patient is having or has recently had an epileptic seizure.

C Evidence of causation demonstrated by both of the following:

1 Headache has developed simultaneously with or soon after onset of the seizure

2 Headache has resolved spontaneously after the seizure has terminated.

D Not better accounted for by another ICHD-3 diagnosis.

Comments:

Well-documented reports support recognition of the subtypes '7.6.1 Ictal epileptic headache' and '7.6.2 Post-ictal headache', according to their temporal association with the epileptic seizure.

Pre-ictal headache has also been described. In a small study of 11 patients with intractable focal epilepsy, frontotemporal headache was ipsilateral to the focus in nine patients with temporal lobe epilepsy (TLE) and contralateral in one with TLE and one with frontal lobe epilepsy. More studies are needed to establish the existence of pre-ictal headache, and determine its prevalence and clinical features, in patients with partial and generalized epilepsy. Pre-ictal headache must also be distinguished from '1.4.4 Migraine aura-triggered seizure'.

7.6.1 Ictal epileptic headache

Previously used term:

Ictal headache.

Description:

Headache caused by and occurring during a partial epileptic seizure, ipsilateral to the epileptic discharge, and remitting immediately or soon after the seizure has terminated.

Diagnostic criteria:

A Any headache fulfilling criterion C.

B The patient is having a partial epileptic seizure.

C Evidence of causation demonstrated by both of the following:

1 Headache has developed simultaneously with onset of the partial seizure

2 Either or both of the following:

(a) headache is ipsilateral to the ictal discharge

(b) headache significantly improves or remits immediately after the partial seizure has terminated.

D Not better accounted for by another ICHD-3 diagnosis.

Comments:

'7.6.1 Ictal epileptic headache' may be followed by other epileptic manifestations (motor, sensory, or autonomic).

This condition should be differentiated from 'pure' or 'isolated' ictal epileptic headache occurring as the sole epileptic manifestation and requiring differential diagnosis from other headache types.

'Hemicrania epileptica' (if confirmed to exist) is a very rare variant of '7.6.1 Ictal epileptic headache' characterized by ipsilateral location of headache and ictal EEG paroxysms.

7.6.2 Post-ictal headache

Description:

Headache caused by and occurring within 3 hours of an epileptic seizure, and remitting spontaneously within 72 hours after seizure termination.

Diagnostic criteria:

A Any headache fulfilling criterion C.

B The patient has recently had a partial or generalized epileptic seizure.

C Evidence of causation demonstrated by both of the following:

1 Headache has developed within 3 hours after the epileptic seizure has terminated

2 Headache has resolved within 72 hours after the epileptic seizure has terminated.

D Not better accounted for by another ICHD-3 diagnosis.

Comment:

'7.6.2 Post-icatal headache' occurs in > 40% of patients with either temporal lobe epilepsy or frontal lobe epilepsy and in up to 60% of patients with occipital lobe epilepsy. It occurs more frequently after generalized tonic-clonic seizures than other seizure types.

Original proposed criteria for ictal epileptic headache (IEH)

Diagnostic criteria A–D must all be fulfilled to make a diagnosis of 'IEH':

A Headache lasting minutes, hours or days.[1]

B Headache that is ipsilateral or contralateral to lateralized ictal epileptiform EEG discharges (if EEG discharges are lateralized).

C Evidence of epileptiform (localized, lateralized, or generalized)[2] discharges on scalp EEG concomitantly with headache; different types of EEG anomalies may be observed (generalized spike-and-wave or polyspike-and-wave, focal or generalized rhythmic activity or focal subcontinuous spikes or theta activity that may be intermingled with sharp waves) with our without photoparoxysmal response.

D Headache resolves immediately (within a few minutes) after intravenous antiepileptic drugs.

Notes

1 A specific headache pattern is not required (migraine with or without aura, or tension-type headache are all admitted).

2 Any localization (frontal, temporal, parietal, occipital) is admitted.

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(37) published 16 potential cases of IEH from a large multicentric neuropaediatric sample. All 16 patients displayed focal or generalized 'ictal EEG abnormalities' during migraine attacks. A spike or spike-and-wave pattern was the most commonly observed EEG pattern, in both MA and MO, whereas EEG theta activity was, surprisingly, associated exclusively with MA or a 'double migraine pattern' in which MA and MO co-existed. Fourteen of 16 children displayed interictal EEG abnormalities. The use of 'ictal epileptic headache' (2,4) may be preferable to the term 'ictal headache', as suggested by Parisi et al. (36–40,118–121).

Conclusion

Epilepsy and migraine are both episodic functional disorders in which susceptible brain regions are hyperexcitable and attacks begin with hypersynchronous neuronal firing. The two disorders have a clinical, pathophysiological, molecular, and therapeutic overlap. In epilepsy and migraine, various factors can provoke attacks, but how these factors lead to neuronal hypersynchronous activity and the initiation of an attack is not understood. When CSD is the key event in a migraine attack, it is still unclear how a CSD relates to a seizure. The lack of a practical technique directly measuring CSD in humans makes studies addressing these questions difficult.

The association between migraine and epilepsy seems more apparent in children and adolescents, especially in genetic epilepsy syndromes such as juvenile myoclonic epilepsy and benign partial epilepsy of childhood with centrotemporal spikes/rolandic epilepsy. Aversion to visual stimuli, or triggering of attacks through flashes, occurs in both epilepsy and migraine. It is probable that shared genetic mechanisms are responsible for this. Epilepsy later in life is more often related to (new) brain lesions than genetic factors, and therefore the association between migraine and epilepsy may become less strong.

The clinical differentiation between migraine and epilepsy is not always easy. Children, in particular, are likely to have autonomic symptomatology both in epilepsy and in headache attacks: they can have isolated, long-lasting ictal autonomic manifestations, while ictal autonomic manifestations (both in epilepsy and in headache) in adults are usually associated, simultaneously or sequentially, with other motor or sensory ictal signs and symptoms. Key unanswered questions are why some individuals are susceptible to migraine and others to epileptic seizures, and in those susceptible to both migraine and seizures, why attacks manifest as one or the other at different times.

The present classification of conditions in which headache and epilepsy are related (migralepsy, hemicrania epileptic, postictal headache) poses great challenges for the clinician. EEG recordings are not routinely done during presumed migraine attacks, and ictal headache will therefore remain an underdiagnosed condition (122). We are not convinced that the current literature provides clear evidence for the existence of a condition named 'migralepsy', where a migraine attack triggers a seizure.

Therapeutic similarities and differences between epilepsy and migraine raise interesting questions. AEDs act by influencing neurotransmitter or ion-channel function in the brain, thus preventing abnormal depolarizations, and some have been shown to be effective in both epilepsy and migraine. About 60% of patients with epilepsy achieve remission, and no clear differences in efficacy have been demonstrated between drugs with different mechanisms of action. In migraine, however, complete remission is seldom achieved, and the mechanism of action seems to be related to efficacy. Furthermore, tolerance to drug side effects is better in epilepsy than in migraine.

The clarification of these issues, as well as of the underlying mechanisms between these two disorders, may allow both fields (epilepsy and headache) to learn lessons from each other, in order to improve clinical diagnosis and therapeutic strategies.

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13

Migraine and vertigo

Yoon-Hee Cha

Introduction

A relationship between migraine and vertigo has been acknowledged for over a millennium, with common references to vertigo and migraine dating back as early as the fifth century by the physician Caelius Aurelianus to one of the fullest descriptions of this relationship by Edward Liveing in 1873 (1,2). Although the etymological connection did not start out intentionally, the English word *megrim* at various points in history meant 'hemicrania', 'dizziness (in humans)', 'low spirits', and 'vertigo (in animals)' (3). However, it was only in the last 150 years that the systematic study of migraine-related symptoms have helped to clarify some of these associations.

In the modern day, vertigo as a symptom of migraine has received more formal recognition by the International Classification of Headache Disorders (ICHD), through its acceptance of vestibular migraine as a migraine subtype in the Appendix section in the third edition (2018) (4). The vestibular symptoms of migraine can be varied and complex, however, and a struggle within the disciplines of neurotology and headache has been in setting limits on the spectrum of what is considered to be vertigo attributable to migraine—limits that have to be set without the availability of biological markers. Like the careful delineation of aura symptoms over time, however, the detailed examination of vestibular symptoms in migraine may also contribute to the overall understanding of migraine physiology.

Definitions

Before embarking on a detailed discussion of migraine and vertigo, a clarification needs to be made that many of the papers referenced in this section do not use the term 'vertigo' in the same way. The International Classification of Vestibular Disorders (ICVD) criteria set forth by the Committee for Classification of Vestibular Disorders of the Bárány Society defined vertigo as the 'the sensation of self-motion when no self-motion is occurring or the sensation of distorted self-motion during an otherwise normal head movement' (5). This illusion may be internal or external, meaning that either the self or the environment may be perceived as moving. The term vertigo was then subdivided into either a 'spinning' illusion or a 'non-spinning' illusion. In contrast, dizziness was defined as 'a sense of spatial disorientation without a false sense of motion'. These definitions were set in 2009, after most papers on migraine and vertigo had already been published.

Most of what is understood about the relationship between migraine and vertigo has been culled through a large body of literature that has used a variety of definitions and terms (6,7). In some works, the term 'vertigo' was narrowly defined as an illusion of actual spinning, whereas in others it has been more broadly used. In some, there was no clear definition of vertigo given. In 2001, Neuhauser and colleagues published criteria for 'migrainous vertigo', defining both a definite and probable form (8). Although many researchers subsequently adopted the Neuhauser criteria in the last decade, a need to more precisely define a migraine–vertigo syndrome was recognized, leading to these recent definitions. As more is learned about the pathophysiology of vestibular migraine, however, these clinical criteria will continue to evolve.

The term 'vestibular migraine' and its diagnostic criteria were established in a consensus paper between the Migraine Classification Subcommittee of the International Headache Society and the Bárány Society (9). Previous terminologies, such as 'migraine vestibulopathy', 'migraine -associated vertigo', 'migraine-related vertigo', and 'migrainous vertigo', were replaced. New criteria for what could fall under the definition of vestibular migraine were developed (**Box 13.1**).

These definitions are now included in Appendix A of ICHD-3, which specifically adapted the definition of vertigo from the ICVD. In adapting the definition of vertigo from the ICVD, only specific forms of vertigo were accepted as falling under the umbrella of vestibular migraine. Specifically, spontaneous, head-motion-triggered, position-triggered, and visually triggered vertigo were accepted. Sound-induced and 'other' triggered symptoms such as those occurring after passive motion, orthostatic changes, medications, heights, and so on, were specifically excluded. In addition, only a diagnosis of *definite* vestibular migraine was included (4).

Epidemiology

Given the recent changes in both the definition and nomenclature of vestibular migraine, we would expect that what is understood to be the prevalence of vestibular migraine to change with time.

Box 13.1 Vestibular migraine

A At least five episodes fulfilling criteria C and D.
B A current or past history of *Migraine without aura* or *Migraine with aura*.
C Vestibular symptoms of moderate or severe intensity, lasting between 5 minutes and 72 hours.
D At least half of episodes are associated with at least one of the following three migrainous features:
  1 Headache with at least two of the following four characteristics:
    (a) unilateral location
    (b) pulsating quality
    (c) moderate or severe intensity
    (d) aggravation by routine physical activity
  2 Photophobia and phonophobia
  3 Visual aura
E Not better accounted for by another ICHD-3 diagnosis or by another vestibular disorder.

Notes:
1 Code also for the underlying migraine diagnosis.
2 Vestibular symptoms, as defined by the Bárány Society's Classification of Vestibular Symptoms and qualifying for a diagnosis of A1.6.6 Vestibular Migraine include:
  (a) Spontaneous vertigo:
    - internal vertigo (a false sensation of self-motion);
    - external vertigo (a false sensation that the visual surround is spinning or flowing)
  (b) Positional vertigo, occurring after a change of head position
  (c) Visually induced vertigo, triggered by a complex or large moving visual stimulus
  (d) Head motion-induced vertigo, occurring during head motion
  (e) Head motion-induced dizziness with nausea, dizziness is characterized by a sensation of disturbed spatial orientation.*

*Other forms of dizziness are currently not included in the classification of vestibular migraine.

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Recently, vestibular migraine was called 'the most frequent entity of episodic vertigo'(10). Prevalence measurements may change owing to a growing recognition of the association between migraine and vertigo, and evolving understanding of the relationship between migraine and actual inner-ear disorders like Ménière disease and benign paroxysmal positional vertigo.

Despite these qualifications, and the range of prevalence statistics cited for vestibular symptoms in migraine, there is unequivocal support for a variety of vestibular symptoms being more common in people suffering from migraine headache than those without. Up to 50–70% of patients with migraine have been reported to suffer from recurrent episodes of dizziness, with about 9–13% experiencing actual vertigo during migraine headaches (11–13). The spectrum of vestibular symptoms experienced by patients with migraine includes spinning vertigo, imbalance, head motion intolerance, visual sensitivity, or motion sickness.

'Vestibular vertigo', defined as rotational vertigo that can be spontaneous or position triggered, or recurrent dizziness with nausea and oscillopsia or imbalance, has been reported at a lifetime prevalence of 7.4% and a 1-year prevalence of 4.9% in a telephone survey involving about a 1000 German citizens (14). In a follow-up analysis of the same population, 3.2% were found to experience both migraine and vertigo in their lifetimes and about 1% specifically met the Neuhauser criteria for migrainous vertigo (15). This is about three times greater than what would be expected by chance. In dizziness clinics, the prevalence of migraine is higher than population baseline; in headache clinics, the prevalence of dizziness is higher than in controls (8).

Natural history

Vertigo associated with migraine appears to follow two different lifetime courses. In the earliest manifestation, a child between the age of 4 and 8 years develops recurrent, usually short episodes of severe dizziness and imbalance. The term *benign paroxysmal vertigo* was first used by Basser to describe this syndrome (16). As very young children often cannot describe their experiences, the combination of severe imbalance with expressions of fear were inferred to be what adults experience as vertigo. In some cases, the child exhibits nystagmus during the episode. In most cases, the episodes last in the order of minutes, but spells that last hours or even days have been reported (17). Despite the term 'paroxysmal' a large proportion of these episodes of vertigo follow a known trigger such as stress, fever, motion, or fatigue (17,18). The association between benign paroxysmal vertigo of childhood and migraine was formally recognized by Fenichel in 1967, and is one of the classical childhood precursors to migraine headaches (19). Whether these children are at higher risk of going on to develop vertigo episodes in adulthood is unknown, but up to 50% of patients in a long-term study were shown to experience continued vertigo into adolescence, and occasionally into adulthood (17). Longer follow-up studies are needed to determine the subsequent burden of vertigo in this population when they become adults.

The second association involves patients with a previous history of migraine headaches, typically starting in adolescence or young adulthood, who subsequently develop episodic vertigo attacks roughly a decade after the headaches start (20,21). In some cases, the vertigo attacks start after migraine headaches have started to decrease, obscuring the association. Vertigo episodes generally decrease with age; new-onset episodic vertigo attributable to migraine appears to be quite uncommon after the age of 50 years (8,21–23). Given the peak age of onset of Ménière disease in the fifth and sixth decades of life and the common occurrence of migraine symptoms during Ménière episodes, ruling out Meniere disease is warranted in the older age group (24).

Genetics

A genetic basis for isolated vestibular migraine in the absence of hearing loss or other causes of imbalance is unknown. However, episodic vertigo, as well as migraine headaches, are much more common in blood relatives of probands with migraine and vertigo than in unrelated spouses (23). Despite the frequency of migraine in patients with spontaneous episodic vertigo, there is so far no evidence that genes implicated in familial hemiplegic migraine (*CACNA1A, ATP1A2, SCN1A*) are involved in vestibular migraine, even in cases of clear autosomal dominant inheritance (25,26).

To date, there has been one case in which a genetic locus has been identified in familial vestibular migraine. A 12.0-Mb region on

chromosome 5q35 with a linkage disequilibrium score of 4.21 was found in a 23-member family in which 10 were diagnosed with migrainous vertigo (27). No gene has been identified in this pedigree and the study has not been replicated. Identity by descent analysis has revealed a possible shared haplotype on chromosome 11q in six of seven affected members of a family with migraine-associated vertigo, but most of these individuals would not meet the current criteria for vestibular migraine (28). Similarly, only a subset of 20 families with benign recurrent vertigo showed linkage to chromosome 22q12 (29). Although 79% of the participants in this study were diagnosed with migraine, the migraine phenotype by itself did not show linkage to this locus. Genome-wide association studies specifically addressing whether progesterone or oestrogen receptor variants may be different in patients with migraine and vertigo versus those with migraine alone revealed one significant single nucleotide polymorphism difference in the PROGINs variant of the progesterone receptor in those with migraine and vertigo (30).

Familial aggregation of episodic vestibular syndromes in the context of migraine have been described. A family with a history of migraine headaches, essential tremor, episodic vertigo, and, in some cases, actual Ménière disease has been reported. Several members of this pedigree responded well to acetazolamide, but a genetic locus was not found (31). One study reported episodic vertigo spells in identical twins, only one of which experienced hearing loss consistent with Ménière disease though both experienced migraine headaches and multiple other family members experienced vertigo and migraine (32).

Given the high frequency of concurrent migraine symptoms with Ménière disease, it may be expected that a genetic susceptibility locus for Ménière disease may also help to elucidate a locus for vestibular migraine. However, of the >20 loci that have been reported for both sporadic and familial Ménière disease, only one has been replicated (33). This locus is in COCH gene, mutations in which can cause DFNA9 (autsomal dominant nonsyndromic sensorineural deafness 9). DFNA9 is associated with progressive sensorineural hearing loss and vestibular dysfunction but is not associated with migraine (34).

Episodic vertigo is frequently a symptom of episodic ataxia, in some cases overlapping with migraine headache. The episodic ataxias are a group of paroxysmal disorders of cerebellar dysfunction in which attacks consist of severe imbalance and dysarthria with variable occurrence of nystagmus or myokymia. Episodic ataxia type 2 (EA2), caused by nonsense mutations in the voltage-gated calcium channel gene *CACNA1A*, is characterized by prolonged attacks of global cerebellar dysfunction (nystagmus, dysarthria, truncal and limb ataxia), during which vertigo can be a prominent symptom (35). A history of migraine headaches is seen in over half of patients with EA2, which is consistent with EA2 and familial hemiplegic migraine type 1 being allelic disorders (36). Clinical descriptions of EA types 1, 3, 4, and 7 have included vertigo without an association with migraine (37–41).

Neurochemical links

Both direct anatomical connections between the vestibular and trigeminal nuclei in the brainstem, as well as shared neurochemical properties within the two systems, support the clinical observation of the co-occurrence of pain and vertigo and the usefulness of some migraine medications in treating episodic vestibular symptoms.

Experimental studies that attempt to co-activate the two systems have shown that inducing facial pain during a motion stimulus enhances nausea, and creating visual vertigo with optokinetic stimulation enhances both facial and body pain sensitivity (42–44). Both monosynaptic pathways between the inferior and medial vestibular brainstem nuclei that synapse with trigeminal nuclei (ipsilaterally and contralaterally) have been described, as well as more elaborate indirect pathways that involve connections between specific subnuclei of both the trigeminal and vestibular systems (45).

Given these close anatomical connections, it is not surprising that similar neurotransmitter receptors are expressed on trigeminal and vestibular ganglion neurons. The main target of triptans—5-hydroxytryptamine (5-HT) receptors 5-HT_{1B}, 5-$HT_{1D,}$ and 5-HT_{1F}—are also expressed on both vestibular and spiral (cochlear) ganglion cells. 5-HT_{1D} and 5-HT_{1F} receptors are specifically expressed on the crista ampullaris of the horizontal semi-circular canal (46). These serotonergic receptors are heavily expressed on arterioles within the vestibular and spiral ganglia (46). This may be one mechanism through which triptans can be used to treat both vertigo and headache (47).

Other ligand-gated channels shared by the two systems include transient receptor potential vanilloid 1 (TRPV1), substance P, calretinin, calcitonin gene-related peptide (CGRP), and the purinergic receptor $P2X_3$ (48). CGRP receptors are specifically located on vestibular efferent terminals (49). One theory regarding the vestibular efferent system is that it functions to regulate the gain of the afferent system (50). Adding CGRP to the lateral line of frogs (a primitive vestibular organ) increases the spontaneous afferent firing rate but reduces the afferent response to cupular deflection (51). Thus, the extravasation of CGRP by pain-afferent terminals during a migraine headache may affect the sensitivity of vestibular afferents. Theoretically, this may lead to true vertigo or intolerance to head motion (52). Similarly, the presence of carbonic anhydrase activity in the epithelial cells surrounding the crista ampullaris and within the supporting cells that surround hair cells may represent a pathway through which drugs like topiramate or acetazolamide may be able to affect vestibular tone and prevent vertigo attacks (31,53–55).

Clinical presentation

A patient with recurrent episodes of vertigo for which migraine is a relevant risk factor may present with vertigo spells in the context of a migraine headache or separate from the migraine headache. Even if a history of migraine headaches is the clear risk factor, a diagnosis of vestibular migraine can only be made if at least two of the episodes of vertigo have occurred temporally with the migraine headache (4). This will present a problem in some cases, particularly in men who may not have a personal history of migraine headaches, but whose episodic vertigo attacks behave qualitatively like migraine headaches in terms of triggers, duration, or response to medications. These patients usually have a strong history of migraine headaches in female first-degree relatives (21). Roughly, 5–25% of patients with vertigo and migraines *always* experience them together, whereas at least two-thirds of patients will experience some vertigo spells with headache and some without (11,20,21,23,52).

Patients may present with aura and migraine as part of the *migraine with brainstem aura* diagnosis, a new entity in ICHD-3, which took

the place of the term *basilar-artery-type* migraine. In every study of episodic vertigo attributable to migraine, only a minority of patients has been found to meet criteria for what was previously termed *basilar-artery-type* or *basilar-artery migraine*. This is mainly because the vestibular symptoms in migraine usually follow a less predictable temporal course than visual aura, are not limited to the 5–60-minute range used to define aura, and frequently occur without headache. Although the vertigo in migraine can range from seconds to days, the most common duration is hours to days. Migraine visual aura, however, appears to occur more frequently in patients who also experience vertigo than those who do not (8,13,20,21).

Clinical examination

The examination of a patient with vestibular migraine is most likely to be completely normal. However, both ictal and interictal ocular motor abnormalities can occur in migraine. These include positional nystagmus that can be horizontal, vertical, or mixed. Nystagmus can be spontaneous or be inducible by head shaking or positional changes. The nystagmus can show either a peripheral or central pattern, or be indeterminant, even in expert hands (56,57). Head-shaking nystagmus can, at times, be 'perverted', meaning that horizontal headshaking can cause vertical nystagmus in migraine, indicating abnormal cross-coupling of head motion information in the brainstem (58). The positional nystagmus, however, is not typical of benign paroxysmal positional vertigo, which occurs in a burst and fatigues.

Ictal downbeat nystagmus has been described in vestibular migraine, which usually localizes to the caudal cerebellum or brainstem (56,59). It should be noted, however, that headache and positional downbeat nystagmus can occur from caudal cerebellar and brainstem lesions (60–62). None of the ocular abnormalities in vestibular migraine should be associated with any other central abnormalities such as ataxia or lateralized neurological deficits. Therefore, a careful evaluation for other neurological signs and symptoms should be made in cases that include central ocular abnormalities and not be presumed to be from vestibular migraine.

Related disorders

Ménière disease

Early in the course of vestibular migraine, it may be difficult, if not impossible, to distinguish from Ménière disease. Triggers and duration can be quite similar between the two (63). Factors that contribute to this difficulty are that Ménière disease typically occurs in mid-adulthood with age at onset in the range of 38–50 years (64,65). The onset of episodic vertigo from migraine typically follows the onset of migraine headache by about a decade, which is close to the lower end of the Ménière age range.

Auditory symptoms such as a feeling of fullness in the ear and tinnitus can occur as part of the migraine syndrome, but it is decidedly uncommon for hearing loss to occur in the context of migraine or for migraine to be associated with progressive hearing loss (66,67). It should be noted, however, that if a patient with recurrent vertigo spells developed a persistent low-frequency hearing loss, they would be diagnosed with Ménière disease regardless of the association with migraine headache. In case series that have noted some progression of hearing loss in vestibular migraine, it has usually been high-frequency sensorineural loss, as seen in ageing. However, there have also been cases of low-frequency hearing loss that were considered to meet criteria for *atypical* Ménière disease, without further clarification of what was atypical in those cases (68).

Complicating the picture further is that Ménière attacks themselves can be associated with severe headache that meet criteria for migraine. One study showed that 56% of patients with Ménière disease had a personal history of migraine and 45% of the attacks experienced by these patients were associated with other symptoms that could be attributable to migraine. In addition to headache, this included photophobia, phonophobia, and even visual aura (24). The baseline prevalence of migraine in patients with Ménière disease has been reported to be in a range that includes no higher than population baseline to over twice that of population baseline (24,69). What appears to be relevant, however, is that patients with a dual history of migraine and Ménière disease tend to present earlier, with a higher tendency for bilateral disease, and a stronger family history of recurrent vertigo (70–72). Genetically identical twins can have one twin affected with Ménière disease and migraine, and the other with episodic vertigo and migraine (32). Therefore, there may, in fact, be more of a continuum in the pathological basis of vestibular migraine and Ménière disease than a clean distinction.

Benign paroxysmal positional vertigo

Patients with migraine have been noted to experience a higher frequency of typical benign paroxysmal positional vertigo (BPPV), as well as experiencing BPPV at an earlier age than people without migraine (73,74). However, positional vertigo that is not BPPV is also part of the vestibular migraine spectrum. Patients with true BPPV may complain of head and neck pain or stiffness, which should not be confused with migraine.

The positional nystagmus of posterior canal BPPV (the variant in 90% of cases) is a burst of torsional upbeat nystagmus beating toward the lower ear during positional testing. The nystagmus starts after a short delay and typically does not last for more than 20 seconds and is effectively treated with the canalith repositioning maneuver (75). In contrast, the positional nystagmus noted in both ictal and interictal vestibular migraine has been noted to be of either a central or peripheral type, but usually has more of a central pattern. One hallmark feature of nystagmus in vestibular migraine is that it is persistent during the entire time that the head is lowered, occurs without a delay, and does not fatigue with repeated positioning (56).

Diagnostic testing

Caloric testing

Vestibular function testing in migraine may be abnormal with or without the presence of vertigo; in some clinical case series, up to 24% of the patients with migraine were reported to have abnormal caloric responses (11,20,52,76–79). In basilar artery migraine, the rate of unilateral paresis is reported to be as high as 60% and the rate of bilateral vestibular paresis as 12% (80,81).

The degree of caloric paresis in vestibular migraine is typically mild and very uncommonly exceeds a 50% asymmetry. Very high degrees of caloric paresis should raise concerns that either there was a problem with the testing (e.g. poor irrigation due to a narrow external canal), or that there is an alternative diagnosis. However, follow-up studies in patients with vestibular migraine show that this disorder can be progressive and be uncommonly associated with bilateral vestibular dysfunction (68).

Vestibular hyper-responsiveness has also been reported in both case–control and longitudinal studies (58,82). These cases are less frequently reported than cases of vestibular hyporesponsiveness. However, they may be in line with a clinical finding that patients who were defined to have definite migrainous vertigo by the Neuhauser criteria, were much less tolerant of vestibular stimulation during caloric testing, and tended to have a stronger history of motion sickness than those with non-migrainous dizziness (58,83).

Vestibular evoked myogenic potentials

The vestibular evoked myogenic potential (VEMP) exam is a test of the otolith–cervical reflex arc and provides complementary information to traditional caloric testing. In caloric testing, the warm and cold water stimulus to the external ear canal changes the direction of endolymph flow in the horizontal semi-circular canal. This deflects the cupula of the horizontal canal either in the direction of the utricle (stimulates) or away (inhibits). This mechanical information is translated into an electrical impulse by the hair cells of the cupula, which travels along the superior branch of the vestibular nerve.

In the VEMP test, a loud sound stimulus in the order of 90–110 dB is presented to the external ear, which stimulates the saccule (an otolith organ) and triggers a saccule–sternocleidomastoid inhibitory reflex. The afferent arc of this reflex travels along the inferior branch of the vestibular nerve (84). The VEMP test has typically been reported as being normal in migraine and vestibular migraine, but a few case series have shown that VEMP responses can show low amplitude, long latency, or even be absent in migraine, particularly in those with migraine with brainstem aura (85–88). To some degree, some of the variability in the reporting of VEMP responses in migraine-related disorders may be due to differences in techniques between vestibular laboratories, as some use higher sound stimuli than others.

Low-amplitude and absent VEMP responses have been shown to be features of migraine, regardless of the presence of vestibular symptoms (87,89,90). Therefore, VEMPs are not a useful test in determining whether vestibular symptoms can be attributed to a migraine syndrome in a patient with pre-existing migraine. VEMPs, however, have been used in research settings to show that migraine is associated with a lack of the normal habituation to repeated sound stimulation typically seen in patients without migraine (89–91).

Audiograms

Audiograms are generally normal in cases of migraine-associated dizziness syndromes that do not clearly fit the criteria of Ménière disease (11,67). Hearing function can decrease with time in vestibular migraine, but usually involves typical high-frequency hearing loss. In cases in which low-frequency loss has also developed, they are considered to be atypical for Ménière disease (68). Hearing thresholds during migraine headaches have been shown to both improve and decline relative to baseline hearing levels (56,92). Hearing loss in what was previously known as migraine with brainstem aura is quite common, noted to be as high as 46% bilaterally and 34% unilaterally (81).

Otoacoustic emissions

Otoacoustic emissions are most commonly used in newborn hearing screening but can also be useful in adults as an additional marker of the intactness of the connection between the cochlear nerve and the inferior colliculi (93). Research on the use of otoacoustic emissions has revealed important differences in the central processing of auditory information in patients with migraine.

When sound energy is transmitted to the inner ear, the cilia of the outer hair cells deflect and emit a tiny fraction of that energy back out of the ear. This tiny otoacoustic emission can be detected by an in-ear microphone (94). When sound is presented to the contralateral ear at the same time, the otoacoustic emission of the ipsilateral ear decreases. In both migraine and vestibular migraine, there is evidence that baseline otoacoustic emissions are low or absent, suggesting peripheral cochlear injury (95,96). There is also evidence of less suppression of ipsilateral otoacoustic emissions with contralateral stimuli, as well as greater variation in suppression, suggesting impairment of central modulation of sound in migraine, regardless of the presence of vestibular symptoms (95,96).

Words of caution

While the growing recognition of vestibular migraine as a frequent and important cause of vestibular symptoms is important and welcome, it is equally important to recognize when vestibular symptoms do not fit this pattern. The following are some guidelines of when to consider an alternate diagnosis before presuming a diagnosis of vestibular migraine.

1. **Patients who complain of baseline imbalance early in the course of their disorder**

   Vestibular migraine is an episodic disorder in which patients should largely be normal in between episodes. One caveat is that patients with migraine often perceive their imbalance to be worse than objective findings indicate (82,97,98). Although mild degrees of balance impairment have been noted interictally in patients with migraine, regardless of whether they also experience vertigo, if chronic balance problems present close to the onset of vestibular symptoms, a careful evaluation for other causes should be performed. For example, patients who experience a severe episode of rotational vertigo lasting for several hours or more and take more than several days to recover should undergo a thorough evaluation for an inner ear disorder.
2. **Head motion-triggered symptoms that have a clear side predominance**

   If symptoms are clearly worse when turning the head to one side versus the other, vestibular function testing should be performed to evaluate a peripheral lesion. If normal, lesions along the central vestibular pathways including the cerebellum should be considered.
3. **Symptoms that are associated with strict unilateral pain in the face or neck.**

This clinical feature should raise concerns for a structural lesion, such as seen in thoracic outlet syndrome, skull-based tumours, vestibular paroxysmia, and complex regional pain syndrome all present with unilateral facial pain and episodic vertigo.

4. **Episodic vertigo associated with any auditory symptoms such as hearing loss, ear fullness, tinnitus, or sound-triggered symptoms**

   This symptom complex should trigger a thorough evaluation for an inner ear disorder and may require a referral to an otolaryngologist. These symptoms should start an evaluation for Ménière disease or, in the right clinical context such as barotrauma, a perilymphatic fistula. In most cases, the auditory abnormalities in inner-ear disorders will be unilateral.

5. **Vertigo episodes that are associated with central ocular abnormalities**

   Although some studies of patients with vestibular migraine have documented central types of ocular abnormalities, including downbeat nystagmus, this is not the norm in vestibular migraine. Interictal central ocular abnormalities like downbeat, upbeat, pure torsional, or gaze-evoked nystagmus should invoke concern for a different central cause.

Management

Abortive treatment

Patients with migraine experience episodes of acute attacks of vertigo, as well as less pronounced vestibular disturbance in between vertigo attacks, such as a tendency toward motion sickness and sensitivity to visual motion. Therefore, a multipronged treatment approach is required.

When the vertigo spells occur, they can be quite debilitating and can take the form of true rotational vertigo, positional dizziness, oscillopsia, or imbalance with nausea. Depending on the symptom and duration, pharmacological intervention may be warranted. Spells that last less than 20 minutes are generally too short for pharmacological treatment, but most vestibular symptoms in vestibular migraine will last on the order of hours. Vestibular suppressants such as promethazine, prochlorperazine, or metoclopramide at standard doses are good first-line agents.

There is relatively less experience in the use of triptans specifically for vestibular symptoms, but the available evidence indicates that they are safe to use using the same guidelines as for headache treatment and can be effective for both vertigo and headache (47). Rizatriptan has been shown to help alleviate rotational chair-induced motion sickness but not visually-induced motion sickness (99,100). Zolmitriptan was used in a clinical trial of migrainous vertigo, but it was underpowered to detect a clinical difference given that only 10 participants were recruited in this placebo controlled trial. However, there were no medication-related side effects noted in its use in treating migrainous vertigo (101).

The vestibular symptoms of migraine usually do not follow the pattern observed for the aura phase of migraine, which makes timing of medication use specifically for the vestibular symptoms challenging. Most patients will experience some episodes of vertigo without accompanying migraine symptoms. In cases in which the spell comes on suddenly and severely, the use of orally disintegrating medication (e.g. sublingual lorazepam), rectal dosing (e.g. prochlorperazine or promethazine), or even cutaneous dosing can be considered (e.g. topical promethazine). Cutaneous dosing tends to be slower and less predictable, however.

Preventative treatment

Preventative treatments for vestibular migraine have generally been similar to those used for migraine headache, starting with recognition and avoidance of triggers. Stress, dehydration, hormonal changes, certain foods, barometric pressure changes, have all been described as triggers for vertigo spells, although none is specific enough to be used as part of the diagnostic criteria for vestibular migraine (9).

There is no evidence from any randomized controlled trials for medications in the preventative treatment of vestibular migraine (102). Similar to the treatment of migraine headache, however, the choice of medication often depends on concurrent issues such as sleep disturbance, mood disorder, or gastrointestinal tolerance. Tricyclic amines, beta blockers, calcium channel blockers, anticonvulsants, and benzodiazepines have all been used successfully in the treatment of vestibular migraine (77,103,104). The anticonvulsants topiramate and lamotrigine have been studied in small trials for their efficacy in vestibular migraine (55,105). In the case of topiramate, 50 mg daily was found to be as effective as 100 mg, with fewer side effects (55).

Some notable differences in the treatment of headache versus vertigo are that calcium channel blockers are more frequently used successfully in the treatment of episodic vertigo than headache (20,106–108). Studies outside of the United States have used flunarizine, lomerizine, and a combination of cinnarizine plus dimenhydrinate, which all have calcium channel blocking properties (20,107,109–111). In the United States, there are reported benefits with other calcium channel blockers (verapamil, diltiazem, amlodipine, nifedipine) (103). It should be noted, however, that calcium channel blocking may be only one of many mechanisms of these medications and it is unclear whether the treatment effect is directly related to the action on calcium channels.

The carbonic anhydrase inhibitor acetazolamide can be quite effective in treating recurrent vertigo, but its effect on migraine headache is unclear owing to a paucity of literature on its use in migraine and indications that it is not well tolerated by patients with migraine (112–113). In the neurological realm, it has proven to be the most useful in EA2, a disorder of recurrent cerebellar dysfunction that is frequently associated with migraine headaches (35). Its use in the clinical scenario of recurrent vertigo and migraine was introduced by Baloh (31), who described its efficacy in a family with recurrent vertigo, migraine, and essential tremor. Whether the mechanism of action is due to its diuretic effect, as a driver of metabolic acidosis, its action on inner-ear hair cells and supporting cells, or some other mechanism, is unknown.

When acetazolamide is used to treat vertigo spells, it should be started at a much lower dose than what is typically used to prevent altitude sickness or treat glaucoma (which starts at 250 mg twice daily or three times daily). Patients with migraine appear to have particular sensitivity to bothersome paraesthesia with this medication (112, 113). The consumption of citric juices to help counteract

the alkalization of urine that promotes the formation of kidney stones may help.

Rehabilitation

There are situations in which a course of physical therapy may be helpful in patients with vestibular migraine, even if they do not have evidence of inner-ear injury. For some patients, desensitization to head movement-induced dizziness and visually induced dizziness, as well as strength and gait training, can be beneficial (114,115). Patients with migraine may also perceive their imbalance to be greater than how they perform on balance tests (116,117). Regaining confidence in walking by learning techniques to avoid falling during dizzy spells may help patients regain the sense of control they need to prevent fear of falling from becoming a distraction. There is also a known comorbidity between anxiety disorder, migraine, and dizziness, a syndrome termed 'migraine anxiety-related dizziness' (or MARD) (118). The anxiety component is important to address because patients with vestibular migraine score higher on anxiety scales, which limits their prognoses for recovery (119,120). Vestibular migraine is recognised as one of the severe potential triggers for the development of persistent postural-perceptual diagnosis, a disorder of chronic imbalance and dizzeiness that is worsened by upright posture and visual motion (121). Rehabilitation along with psychological support can play a strong role in managing the interictal symptoms that contribute to overall morbidity and limit quality of life in patients with migraine and vertigo.

Conclusion

Converging lines of evidence from epidemiological, anatomical, neurochemical, and therapeutic experience in treating patients with migraine and vertigo support a close association between the two phenomena. A complete understanding of one phenomenon is not possible without accounting for the behaviour of the other. It is hopeful that the establishment of criteria for vestibular migraine and the inclusion of vestibular migraine in the ICHD Appendix will facilitate the exploration of the link between migraine and vertigo.

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14

Treatment and management of migraine

Acute

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Introduction

Migraine is a highly prevalent and debilitating primary headache, presenting with recurrent pain attacks, associated symptoms of vegetative disturbance, and hypersensitivity of various functional systems of the central nervous system (1,2). The disease is typically characterized by severe headache attacks, lasting from 1 to 3 days, associated with nausea, vomiting, photophobia, phonophobia (migraine without aura), and, in 20–25% of patients, with neurological aura symptoms (migraine with aura) (3). Migraine can be very disabling and it is a disorder usually underdiagnosed and suboptimally treated worldwide (4–7). Migraine has a huge social and economic impact and an appropriate treatment should be addressed to improve patients' symptoms and diminish the patients' temporary disability (lost time at work or school; inability to perform household work, and to take part in social and leisure activities, or to spend time with family; emergency department visits) in a cost-effective way and with a minimal recurrence rate and adverse effects (3).

An effective migraine treatment should be started only when the correct diagnosis is reached, according to the International Classification of Headache Disorders-3 criteria (8). All national and international guidelines recommend making a plan of care based on the patient's preferences and expectations (9–14). A thorough explanation should be offered by the clinician, ruling out all the alternative life-threatening conditions that the patient is concerned about. It has to be made clear to patients that their headache is not caused by a structural disorder (15).

An appropriate treatment consists of pharmacological agents along with the integration of non-pharmacological approaches. Avoidance of triggers such as stress, alcoholic beverages, insufficient sleep, some specific foods, frequent travelling/jet lag, skipping meals, and so on, should be recommended (16). Other triggers such as changes in weather conditions and temperature, or hormonal changes in women, are not controllable by the patient (see also Chapter 7). For monitoring progression of disease and acute treatment after initiating therapy, a headache diary could be very useful. Triggers and potential triggers, headache frequency, intensity, and medication usage should be recorded by the patient (10,15).

Other important non-pharmacological approaches include relaxation training, biofeedback, and lifestyle modification (getting adequate sleep and exercise, stopping smoking, avoiding alcoholic beverages) can significantly impact a patient's overall headache disability (10). During an acute attack some non-pharmacological measures are useful and could help some patients: avoidance of uncomfortable sensory stimuli, rest in a dark and quiet room, ice packs over the head or applying pressure over the superficial temporary artery on the same side as the pain (15).

Goals of management and treatment

Although, migraine cannot be cured, it can be effectively managed in most cases (11). Periodic follow-up of medical management is required. At each visit, doctors should discuss with patients all benefits and side effects of the treatment. The patient's headache diary should be examined carefully. Education of migraine sufferers about their condition and its treatment is crucial part of the management of this disease (9–15).

Two different pharmacological strategies are available for treating and preventing this troublesome disorder—abortive/acute and prophylactic. Both approaches are often needed for patients with frequent and severe migraine attacks (9–15). Acute headache medication is the best option in patients with infrequent attacks and/or bad compliance. In most cases, if the patient has infrequent attacks and is well controlled by acute treatment, preventive medication is not needed (10). The aim of acute medications is to relieve or stop the progression of the attack, eliminating the pain and associated symptoms. It is very important to individualize the treatment and develop a treatment strategy taking into consideration all factors such as co-existent illnesses, the patient's age, type of migraine, severity and disability of the attacks, and associated symptoms (**Box 14.1**). Medication choice for a patient with migraine must be always individualized. There are two basic strategies for the acute

Box 14.1 Factors determining the drug of choice and/or the drug dose

1 Age of patient.
2 Pain intensity of attack.
3 Rapidity of symptom onset.
4 Duration of attack.
5 Associated symptoms.
6 Concomitant diseases.
7 Special conditions (gestation).
8 Previous treatments experience.

treatment of migraine: step care and stratified care. In step care we recommend that drugs across or within attacks are escalated from simple analgesics to specific migraine therapies. Stratified care bases treatment selection on an initial assessment of illness severity. The stratified care approach is associated with better acute treatment efficacy and may be the most appropriate for many patients with severe migraine attacks (17). Treatment selection is based on the patient's headache characteristics, including frequency, severity of attacks, associated symptoms such as nausea and vomiting, and extent of disability (using instruments like the Migraine Disability Assessment Questionnaire) (17,18). Migraineurs with minimal or no disability may be well controlled only by non-specific treatment, while patients with significant disability may be prescribed a specific acute and/or preventive treatment medications (10,14).

Medication for an acute attack can be specific or non-specific. Specific medication is useful only for migraine attacks, and non-specific medication can also control other pain disorders. Migraine-specific agents include ergotamine, (dihydroergotamine (DHE)) and triptans. Non-specific agents are non-steroidal anti-inflammatory drugs (NSAIDs), combined analgesics, antiemetics, opioids, and corticosteroids. Non-specific agents (NSAIDs, combined analgesics, and antiemetics) are indicated for mild or moderate attacks. Specific agents are used for the treatment of moderate-to-severe migraine and in patients whose mild-to-moderate migraine responds poorly to NSAIDS or combined analgesics. When choosing medication, it is also very important to select an adequate formulation and route of administration, based on severity of the attack, need for rapid relief, or the presence or absence of nausea or vomiting. In the cases with severe nausea or vomiting a non-oral route and antiemetic medication are recommended (10).

In the selection of the drug, treatment attributes (19) and preferences of the patients are also important (20). For doctors, the efficacy attributes are more important than tolerability or consistency (19). For patients, the most important attributes of a migraine medication are complete relief of pain, lack of recurrence, and rapid onset of pain relief. Consistency and lack of adverse events are also considered of great importance.

Another key question is when to start the treatment of the migraine attack (21). The evidence supporting early application comes from studies of triptans. After the first study with sumatriptan (22), which showed that early treatment is associated with better pain-free rates, data confirming this strategy were published for almost all the triptans. This treatment approach has been also positive when combining triptans with NSAIDs (23), and seems to be cost-effective (24). The pain-free efficacy of triptan therapy is enhanced when treating mild attacks versus moderate-to-severe attacks. Therefore, treating the attack when the pain is mild improves treatment efficacy. Some controversies remain regarding the initiation of treatment during the mild phase of a migraine episode. For example, the early treatment approach may not be suitable for all migraine sufferers, as attacks are highly variable and tension-type headache commonly co-occurs. However, early intervention can improve treatment outcomes and prevent central sensitization and attack progression. It can also increase patient satisfaction (21). One of the disadvantages of this strategy is that it can induce frequent intake of medications and increase the risk of medication overuse. Medication overuse headache has to be prevented. Acute headache medication overuse often causes treatment failure; for this purpose it is crucial to educate the patient how to use acute agents. To avoid medication overuse headache, it is important to limit the acute headache treatment to 2 days per week (acute treatment should not be taken for more than 9 days per month) and use preventive treatment in patients taking acute agents for 1 or more days per week. The desirable goal for acute migraine treatment from a clinical and patient perspective is the rapid and sustained complete removal of pain and restoration of normal functionality. In Box 14.2 we summarize some of the relevant points that have to be taken into account when selecting a symptomatic treatment.

Specific treatment

Specific acute headache medications include ergotamine, DHE, and selective 5-hydroxytriptamine (5-HT_1) agonists/triptans (Table 14.1) (9–15).

Box 14.2 Ten basic points for the selection of a symptomatic treatment of migraine

1 In the clinical practice setting, this is the only management option that most patients really do need.
2 Symptomatic treatment should be optimized at its maximum before recurring to prophylactic therapy.
3 In the aim of avoiding medication abuse, symptomatic treatment should never be authorised as a single management option if the patient experiences 10 or more days of pain per month
4 Any symptomatic treatment should be tailored to each patient's needs and each crisis' characteristics: not every patient requires the same management for all episodes.
5 When it comes to individualizing treatment, the type of migraine and its co-existence with other headaches should be considered.
6 The presence of concomitant disorders and the previous experience of the patient regarding symptomatic treatment are key elements at the time of selecting a specific pharmacological approach.
7 The existence of digestive-related associated symptoms (nausea, vomiting) suggests the need of early administration of prokinetic and antiemetic medications.
8 The main reason for treatment failure comes from the use of not sufficiently efficient medications.
9 The choice of administering a certain medicine through an inadequate formulation (i.e. oral formulation in patients with vomiting episodes) is another frequent reason for treatment failure.
10 Early management of all episodes is highly recommended.

Table 14.1 More common specific drugs used as acute/abortive treatment in migraine attacks

Drug	Dose	Route of administration	Advantages	Disadvantages
Ergots	Dihydroergotamine: parenteral 0.5–1 mg; intranasal Ergotamine: 1–2 mg in suppositories	Intravenous, intranasal, rectal	Low price Good efficacy Can be combined with antiemetics	Elevated risk of overuse Can increase nausea and vomiting
Triptans	Depending on type of triptan and route of administration • Sumatriptan: • Sc: 6 mg • oral 50–100 mg, inhaled 10–20 mg, rectally 25 mg, transdermal patch 6.5 mg • Almotriptan oral 12.5 mg • Zomitriptan oral and oral dispersible 2.5–5 mg, intranasal 5 mg • Eletriptan oral 20–80 mg • Naratriptan oral 2.5 mg • Rizatriptan oral and oral dispersible 5–10 mg • Frovatriptan oral 2.5 mg	Oral, oral dispersible, subcutaneous, intranasal, rectal	The group with highest efficacy. Specific treatment for migraine. Able to relieve severe migraine attacks and associated symptoms (nausea and vomiting) Can be combined with NSAIDs and simple analgesics Different non-oral routes of administration available	Expensive Not recommended in patients with elevated cardiovascular risk

NSAID, non-steroidal anti-inflammatory drug.

Acute treatments taken at the start of the attack are a mainstay of migraine management and this is the best approach in the majority of migraineurs (10,25).

The first drugs used for migraine were simple analgesics with no migraine-specific mechanism of action, such as aspirin, which is still widely used (26). Next, ergotamine was isolated from ergots in 1918 (27) and introduced in migraine therapy in 1925 because of its presumed sympatholytic activity (28). The modern era of migraine treatment started with the synthesis of the potent 5-HT antagonist methysergide from LSD25 by Sandoz in Basel, Switzerland (29). Nowadays, triptans and ergots are the only available migraine-specific abortive medications.

Table 14.1 summarizes the more frequent specific drugs used in acute migraine.

Ergots

Ergot alkaloids, such as ergotamine or DHE, have been the only 'specific' treatment for migraine for decades. Ergots have their 5-$HT_{1B/D}$ receptor agonist action in common with triptans, and that is the concept responsible for the control of migraine-related pain. They interact with many other receptors such as 5-HT_{1A}, 5-HT_2, 5-HT_5, 5-HT_7, α-adrenergics, and dopamine D2, which is the reason for their varied profile of adverse effects, the most common of which are nausea and vomiting. Other frequently observed adverse effects are cramps, sleepiness, and transitory muscular pains of the inferior limbs. The most feared ergotamine- and DHE-derived secondary effects are the cardiovascular ones. Elevations in blood pressure have been described, added to cases of angina/heart attack and ischaemia of the lower limbs. A chronic use of ergotamine is associated with some specific adverse effects. A remarkable one comes from ergotamine's capacity (and from caffeine incorporated in those formulations, which is authorised in some countries) to induce rebound headache and trigger the feared ergotic overuse headache. Ergotics are still the cause of one-third of the overuse headache in some countries (30). The efficacy of ergotamine could be positioned in a middle line between NSAIDs and triptans. One of its most serious disadvantages is its low bioavailability (1% orally, maximum 3% rectal), reason enough for the limited level of efficacy. As triptans exhibit a larger efficacy and a better, cleaner profile, expert consensus concluded that ergotic products are not indicated among de novo migraine patients, a group in which triptans should always become first choice (31). In this sense, ergotic medicines could be maintained in those patients who have used them for a long time; who express a satisfactory response and do not present contraindications; and whose frequency of attacks is low (no more than one per week). An additional indication for ergots could be directed to some patients with long attacks and high rates of pain recurrence.

One option in these cases is the administration of ergotamine rectal suppositories (1–2 mg) with an antiemetic (10 mg metoclopramide oral tablets, or 25–100 mg chlorpromazine or 25 mg prochlorperazine rectal suppositories if the patient is vomiting). Up to six (1 mg) tablets can be taken or two suppositories over 24 hours for an individual attack. Use should be restricted to one dosage day per week (9).

DHE is available in 1 mg/ml ampules, for intramuscular (IM), subcutaneous (SC), or intravenous (IV) administration, or nasal spray in some countries (15). In clinical trials DHE nasal spray has been superior to placebo, similar to ergotamine and inferior to subcutaneous sumatriptan, and therefore in some guidelines this is considered as an alternative in selected patients with migraine (9,13). Ergot compounds, in most of the guidelines published, are considered second-line treatment agents in migraine attacks (9,11,13).

Most of the studies support a therapeutic role of IV and IM administration of DHE in emergency settings. DHE is initially administered at a test dose of 0.5 mg (0.25 mg for children) given via IV push over 3–5 minutes. If the headache persists, another 0.5 mg DHE is given and 1.0 mg DHE is administered every 8 hours. If nausea persists, the next dose can be reduced to 0.25 mg. DHE is tapered down and discontinued in 3–5 days if the patient is headache-free or fails to respond to the medication (15).

An antiemetic should be added to parenteral DHE. An effective treatment option is to administer 0.5–1 mg IV DHE with 10 mg IV metoclopramide or prochlorperazine (the latter, given alone, is able to reverse a migraine episode by itself in some cases) (32–34).

An orally inhaled and self-administered formulation of DHE delivered to the systemic circulation (known as MAP0004), has

been developed. MAP0004 aerosol DHE provides desirable activation of 5-$HT_{1B/1D}$ receptors, resulting in an effective antimigraine effect. Unlike IV DHE, MAP0004 is less likely to bind with other serotonergic, adrenergic, and dopaminergic receptors, resulting in fewer side effects. MAP0004 administered alone shows no statistically significant drug-related increase in nausea compared with conventional IV DHE, which is generally administered with an antiemetic medication. MAP0004 is less arterio-constrictive than intravenous DHE. MAP0004 has been proven to be effective and well tolerated for acute migraine treatment. It provides statistically significant pain relief and freedom from photophobia, phonophobia, and nausea compared with placebo. Both phase II and III clinical trials support its antimigraine efficacy. MAP0004 has a superior tolerability to IV DHE. MAP0004 may be a promising first-line agent for migraine treatment, with lower rates of nausea and vomiting than other DHE routes of administration (35–37).

The use of ergots is contraindicated when renal or hepatic failure is present, and in pregnancy, high blood pressure, sepsis, and coronary, cerebral, and peripheral vascular disease (38). Some formulations have been banned by the US Food and Drug Administration (FDA), due to their severe adverse effects.

Triptans

It was known that 5-HT was decreased in blood during a migraine attack and infusion of 5-HT was shown to relieve migraine attacks (39). The studies focusing on the importance of 5-HT inspired the development of sumatriptan by Patrick Humphrey from Glaxo (40).

Triptans are 5-HT agonists with a high affinity for 5-HT_{1B} and 5-HT_{1D} receptors. Triptans were originally thought to provide migraine relief by causing cranial vasoconstriction, most likely through action at postsynaptic 5-HT_{1B} receptors on the smooth muscle cells of blood vessels. But it is well known that triptans also block the release of vasoactive peptides from the perivascular trigeminal neurons through their action at presynaptic 5-HT_{1D} receptors on the nerve terminals. In addition, triptans bind to presynaptic 5-HT_{1D} receptors in the dorsal horn, and this binding is thought to block the release of neurotransmitters that activate second-order neurons ascending to the thalamus. Triptans may also facilitate descending pain inhibitory systems (41).

Subcutaneous sumatriptan was the pioneer drug in class and was introduced into clinical practice in 1992 after it was proved to relieve both migraine and associated symptoms like nausea and vomiting, being superior to placebo in all efficacy parameters (42). After this first publication many thousands of patients have been included in clinical trials with oral triptans (43,44).

At present, there are seven triptans available: sumatriptan, rizatriptan, zolmitriptan, naratriptan, almotriptan, eletriptan, and frovatriptan. All of them are shown to offer a favourable response versus placebo, both for headache response and sustained pain-free response (45–47).

Several clinical trials have demonstrated the superiority of triptans over ergots and NSAIDs (43). The triptans became the initial treatment choice for acute migraine attacks, when the headache is moderate to severe and there are no contraindications for their use. They are prescribed as first-line therapy for severe migraine attacks and as back-up medication for less severe attacks that do not adequately respond to simple analgesics (9–14). All triptans are available as oral tablets. In an effort to deliver more rapid onset of pain relief, a variety of formulation alternatives to oral triptan conventional tablets have been developed, including nasal sprays, suppositories, and rapidly dissolving oral wafers. Different ways of administration can be used when nausea and vomiting are present.

Sumatriptan

Sumatriptan is available as a SC injection, an oral tablet, a nasal spray, a dispersible tablet, a transdermal patch, a rectal suppository, and a breath-powered powder intranasal formulation.

It is the only triptan that can be administered as a SC injection, meaning it is the fastest available triptan, as it avoids the gastrointestinal tract and is rapidly absorbed. It works very quickly to relieve pain (>80% headache relief at 2 hours), nausea, photophobia, phonophobia, and functional disability, but it is associated with frequent adverse events (48).

Therefore, SC sumatriptan is the ideal triptan for patients who need rapid relief or have severe nausea or vomiting. The SC administration of sumatriptan may cause pain in the site of injection, flushing, burning, and hot sensations. Dizziness, neck pain, and dysphoria can also be seen. These adverse events normally disappear in around 45 minutes.

Almost 80% of patients experience pain relief from the initial SC administration, but headache recurs in about one-third of the patients within a day. These patients respond well to a second dose of sumatriptan and sometimes to simple or combined analgesics, but a second dose of oral sumatriptan does not prevent the recurrence (49).

Oral sumatriptan is used for headaches with gradual onset when rapid pain relief is not required; it is available in doses of 100 mg, 50 mg, and in some countries in 25 mg; doses of 50 mg and 100 mg are clearly superior to 25 mg. The headache response at 2 hours for both doses (50 mg and 100 mg) is around 60%.

Sumatriptan is also available as a dispensable tablet; in the studies comparing this formulation with placebo, the results were superior to the conventional tablets.

Sumatriptan 25 mg administered rectally is also an effective treatment for headache relief and functional disability reduction, but the clinical data are limited because this method of administration is not available in many countries (50).

Similarly, intranasal sumatriptan is effective as an abortive treatment for acute migraine attacks, relieving pain, nausea, photophobia, phonophobia, and functional disability (51). Although their effect depends partially on nasal mucosal absorption, a significant amount of the drug is swallowed. It transits the stomach and is then absorbed in the small intestine. Thus, its action also depends on gastrointestinal absorption with the limitations of the oral triptans (52).

The transdermal route of administration by using transdermal iontophoretic patches was approved by the FDA. This method of application bypasses hepatic first-pass metabolism and avoids gastric transit delay. An excellent tolerability (with no triptan-related adverse events) and superior efficacy versus placebo was demonstrated (53). Transdermal sumatriptan was superior to oral triptans for patients with migraine whose nausea is the reason for the delay or avoidance of acute treatment (54). The patches are a promising choice of treatment for patients with intolerable triptan-related adverse events, as well as for migraineurs with disabling vomiting and poor absorption of oral medication (55).

A needle-free device for sumatriptan injection is available in the USA with an efficacy similar to traditional SC administration (56). Also, a new formulation of breath-powered powder sumatriptan for intranasal administration has recently been approved by the FDA. The administration of sumatriptan with this system provides an early onset of efficacy (it is superior to oral sumatriptan at 15 and 30 minutes) with low systemic drug exposure and few triptan-associated adverse events (57).

All these non-oral routes of administration offer a useful alternative delivery system for patients who have difficulty swallowing conventional tablets and for patients whose nausea and/or vomiting impede the swallowing of tablets and/or make the likelihood of complete absorption unpredictable. These alternative formulations offer migraineurs the possibility of using abortive treatment at the onset of migraine attacks without the need of liquids, anytime and anywhere.

Zolmitriptan

Zolmitriptan was the second triptan introduced to the market. It is available in oral doses of 2.5 and 5 mg in conventional and dispersible tablets. It has a high oral bioavailability (40%) and a T_{max} of around 2.5 hours. It is comparable to sumatriptan in terms of efficacy and tolerability. Zolmitriptan 2.5 mg and 5 mg oral tablets are effective in achieving pain relief within 2 hours (around 60% of patients) following treatment. Both doses are comparable, but the zolmitriptan 5 mg tablet is superior to the zolmitriptan 2.5 mg tablet in achieving 1- and 2-hour pain-free responses (58).

Zolmitriptan as a nasal spray formulation has a proven efficacy, high tolerance, and a very fast onset of action. Zolmitriptan has been detected in plasma only 2 minutes after intranasal administration versus 10 minutes after oral administration, thus achieving faster migraine relief than oral zolmitriptan. It is the triptan with the highest nasal absorption (about 30%). It was found to provide pain relief in some patients as soon as 15 minutes after administration (59). Good candidates for this treatment formulation are migraineurs whose pain escalates rapidly from moderate to severe, and those who have quick time to vomiting or have failed treatment with oral triptans (60).

Naratriptan

Naratriptan has a long half-life and a long T_{max}. It is available 2.5-mg tablets. It has the lowest range of efficacy at 2 hours, with a headache response of 48%. Relief rates are lower than with the other triptans, but it is very well tolerated. It could be an alternative in patients with mild or moderate attacks, or in patients with tolerability problems with other triptans. The efficacy of naratriptan 2.5 mg versus NSAIDs has not been sufficiently investigated (61). It could have some efficacy in preventing migraine during prodromal phase, but the evidence is low (62).

Rizatriptan

Rizatriptan is a second-generation triptan available in 10 mg and 5 mg tablets, or as an orally disintegrating tablet (wafer) formulation (63). It is rapidly absorbed from the gastrointestinal tract and achieves maximum plasma concentrations more quickly than other triptans (shorter T_{max}), providing rapid pain relief and a high headache response (69%). Clinical trials have shown that rizatriptan is at least as effective or superior to other oral triptans and has more consistent long-term efficacy across multiple migraine attacks. Rizatriptan is superior to placebo in achieving total migraine freedom (freedom from pain and absence of associated symptom) dose across all treatment paradigms (64). It has a higher recurrence rate than other triptans. Rizatriptan has a significant interaction with propranolol, which is why the dose in patients using this drug should be 5 mg. Patients whose attacks rapidly evolve from moderate to severe pain are good candidates for rizatriptan (10).

Almotriptan

Almotriptan is available in oral tablets of 12.5 mg. It shares two common characteristics with sumatriptan: it does not cross the blood–brain barrier and does not produce active metabolites (65). The headache response at 2 hours is 61%. In comparative trials the efficacy has been similar to that of sumatriptan, with better tolerability (similar to placebo), which has been confirmed in clinical practice (66). A secondary finding in these trials was that patients who took almotriptan early, when the pain was still mild, achieved better outcomes. This prompted the initiation of studies designed to assess the effect of almotriptan in early intervention. Open-label trials reported improvements in pain-free end points (2 hours and 24 hours), and subsequent randomized clinical trials confirmed these findings (67). Almotriptan combines good efficacy with excellent tolerability.

Eletriptan

Eletriptan is a second-generation triptan with favourable bioavailability and half-life, a high affinity for $5\text{-HT}_{(1B/1D)}$ receptors and selectivity for cranial arteries (68). The headache response at 2 hours was 60% for the 40-mg dose and 63% for the 80-mg one. Eletriptan (40 mg and 80 mg) has been shown to be effective as soon as 30 minutes after administration and it is well tolerated when compared to placebo (69). In comparative clinical trials, eletriptan 40 mg and 80 mg were superior or equivalent to other triptans and have shown lower recurrence rates than other triptans (70). The incidence of minor harm was dose dependent, with 80 mg resulting in significantly more adverse effects than 40 mg. A patient with moderate-to-severe attacks and a tendency to recurrence could be a good candidate for eletriptan.

Frovatriptan

Frovatriptan is an orally administered triptan at doses of 2.5 mg. It has a very long half-life (approximately 26 hours) and the lowest headache response at 2 hours (44%). In randomized trials it was superior to placebo and it was generally well tolerated, with an adverse event profile similar to placebo. Frovatriptan provides an alternative treatment in patients who have had adverse events or frequent headache recurrences (71). If frovatriptan 2.5 mg is taken twice a day during the period of increased migraine vulnerability associated with menstruation, migraine attack occurrence in patients with menstrual migraine is significantly reduced (72). Frovatriptan is established to be effective for the short-term prevention of menstrually associated migraine (73,74).

Triptans are an appropriate first-line acute treatment of moderate-to-severe migraine in patients without contraindications such as ischaemic heart disease, angina pectoris or uncontrolled hypertension. For safety, an electrocardiogram is recommended for patients over 40 years of age with risk factors for heart disease (10). Adverse

events like fatigue, dizziness/vertigo, asthaenia, and nausea can be observed with all triptans. The incidence of adverse events is dose dependent with rizatriptan and zolmitriptan. Transient chest symptoms have also been reported for all treatments in this class. There is also a risk of serotonin syndrome, when triptans are taken together with other serotonin agonists. The only disadvantage of the use of triptans is their high cost compared with ergots (12,13). Triptans and ergots are both contraindicated when a cardiovascular disease is present (10–15). Triptan product monographs typically state that they are contraindicated in patients with hemiplegic, ophthalmoplegic, and basilar migraine; these contraindications are theoretical and based on the actions of vasoconstrictors. In small clinical trials, the use of triptans during the aura phase appears to be safe but does not prevent the headache. Because of this, patients with migraine with aura should be advised to take their triptan at the onset of the pain phase. However, if patients find that treatment during the aura is effective, there is no reason to discourage this practice (13).

Early triptan intake after headache onset may help to improve the efficacy of acute migraine treatment (75).

Nowadays, there are seven different triptans available on the market with level A evidence for treatment of migraine attack (76). All of them are similar when it comes to their mechanisms of action or pharmacodynamics, but they are quite diverse in their pharmacokinetic profiles, which make them suitable for use in different types of attacks. Several meta-analysis have been published comparing the different triptans with regard to different parameters, such as headache response, pain-free rate, recurrence rate, tolerability, and so on (45–47,77). Based on this knowledge and clinical practice, we can make some recommendations for the use of the different triptans (Table 14.2). It is important to know that the response from one particular patient to one particular triptan is unpredictable and oral triptan therapy does not provide headache relief in one-third of patients. Because of this, in case of no response to one triptan or poor tolerability, other triptans should be tried over time in subsequent attacks.

Migraine patients have to be educated well so that they give up inadequate practices or unjustified prejudices about triptan use (15). Triptans are vasoconstrictors and are contraindicated in patients with coronary and cerebrovascular diseases but have been proven remarkably safe in people without vascular disease. There has been concern about serotonin syndrome in patients taking triptans and selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors concomitantly. Although clinical experience indicates that serotonin syndrome is extremely rare with triptan use, patients should be informed about its symptoms.

Triptans combined with NSAIDs

Multiple peripheral and central mechanisms may be involved in migraine and a drug combination may potentially achieve better response rates by combining different drug targets (78).

After some open clinical observations (79) and the first clinical trial (80), in which the combination of sumatriptan and naproxen sodium was superior to sumatriptan alone, 12 studies have been published testing the combination of sumatriptan 50mg or 85 mg plus naproxen 500 mg to treat attacks of mild, moderate, or severe pain intensity. Using 50 mg sumatriptan rather than 85 mg in the combination did not significantly change the results. Treating early, when pain was still mild, was significantly better than treating once pain was moderate or severe for pain-free responses at 2 hours and in the 24 hours post-dose. The combination seems to reduce the risk of headache recurrence. Where the data allowed direct comparison, combination treatment was superior to either monotherapy, but adverse events were less frequent with naproxen than with sumatriptan (81).

The association of frovatriptan 2.5 mg with 25 or 37.5 mg dexketoprofen was superior to frovatriptan alone in initial efficacy at 2 hours while maintaining efficacy at 48 hours in in a randomized trial (82).

The combination of triptan with NSAIDs is an alternative in cases of triptan failure or frequent recurrence.

Table 14.2 Potential indications for each of the different triptans available

Compound	Formulation	Indication
Sumatriptan formulations	Subcutaneous 6 mg	Severe crises resistant to oral and nasal formulations
	Nasal 20 mg	Crises resistant to oral administration Patients with vomiting episodes
	Nasal 10 mg	Children and adolescents
	Oral 50 mg	Standard migraine patient Patients with potential risk of pregnancy
Zolmitriptan	Oral 2.5 mg and 5 mg	Standard migraine patients
	Nasal 5 mg	Crises resistant to oral administration Patients with vomiting episodes
Naratriptan	Oral 2.5 mg	Long-lasting low-to-moderate crises Adverse effects present with other triptans
Rizatriptan	Oral 10 mg	Serious, fast, short-lasting crises
Almotriptan	Oral 12.5 mg	Standard migraine patients Secondary effects present to other triptans
Eletriptan	Oral 20 mg and 40 mg	Severe long-lasting crises
Frovatriptan	Oral 2.5 mg	Long-lasting low-to-moderate crises

Non-specific treatment

Over-the-counter (OTC) analgesics are the most used medications for migraine attacks, although their efficacy is limited. However, using the stratified approach, migraine attacks with no more than mild attack-related disability may be treated with non-specific medications.

Non-specific treatment options are also considered when contraindications or side effects related to specific medications are present and when there is a limited supply of these medications; cost issues could be important in some cases and represent the first line in the therapy of migraine in milder attack (83).

Analgesics and NSAIDs

Sometimes first-line acute treatments of migraine include a variety of oral analgesics. If there is no substantial disability present, most patients obtain pain relief by using simple analgesics (9–14).

NSAIDs are among the most commonly prescribed medications in the world. NSAIDs are non-specific medications for acute treatment of migraine. They are used for their anti-inflammatory, antipyretic, antithrombotic, and analgesic effects, which may be due to some inhibitory function on both peripheral trigeminal neurons and central neurons (84). The most frequent non-specific drugs are summarized in Table 14.3.

Various NSAIDs (including ibuprofen, naproxen sodium, diclofenac potassium and others) have been tested in acute migraine. In most trials with OTC medications, patients with severe attacks or frequent vomiting were excluded. Apparently, there are no differences in efficacy between the different NSAIDs, but there is a lack of head-to-head comparators. NSAIDs are effective for mild-to-moderate attacks and in some patients could be effective also in severe attacks.

NSAIDs should be avoided in patients with gastric ulcers, renal failure, high risk of bleeding, and acetylsalicylic (ASA)-induced asthma (85).

Aspirin

Acetylsalicylic acid (ASA) (900 mg or 1000 mg) has been tested in several trials alone or in combination with metoclopramide 10 mg and compared with placebo or other active comparators, mainly sumatriptan 50 mg or 100 mg. In all studies it has been superior to placebo and similar to sumatriptan 50 mg. Adverse events were mostly mild and transient, occurring slightly more often with aspirin than placebo. Additional metoclopramide significantly reduced nausea and vomiting compared with aspirin alone but without differences in efficacy (86).

Naproxen sodium

Naproxen (500 mg and 825 mg) was better than placebo for pain-free response and headache relief in the clinical trials. Analysing only the lower dose of 500 mg of naproxen did not significantly change the results. Adverse events, which were mostly mild or moderate in severity and rarely led to withdrawal, were more common with naproxen than with placebo when the 500 mg and 825 mg doses were considered together, but not when the 500 mg dose was analysed alone.

The only concern is that for naproxen the number needed to treat (NNT) of 11 for pain-free response at 2 hours suggests that it is not a clinically useful treatment. Compared with other commonly used analgesics for acute migraine, naproxen is inferior for the same outcome (87), although in clinical practice the efficacy of naproxen sodium is not different from other triptans.

Ibuprofen

Ibuprofen has been tried in doses of 200 and 400 mg. Both doses are superior to placebo, but the higher dose was significantly better than the lower dose for 2-hour headache relief. Soluble formulations of ibuprofen 400 mg were better than standard tablets and provided more rapid relief. Similar numbers of participants experienced adverse events, which were mostly mild and transient, with ibuprofen and placebo. Ibuprofen is an effective treatment for acute migraine headaches, providing pain relief in about half of sufferers but complete relief from pain and associated symptoms only for a minority (88).

Diclofenac potassium

The number of patients included in the studies with oral diclofenac is low, but it allows establishment of the efficacy of oral diclofenac potassium at a dose of 50 mg as an effective treatment for acute migraine, providing relief from pain and associated symptoms, although only a minority of patients experience pain-free responses. There were insufficient data to evaluate other doses of oral diclofenac, or to compare different formulations or different dosing regimens, although the oral powder solution seems to have a quicker onset (84). Adverse events are mostly mild and transient and occur at the same rate as with placebo (89).

Paracetamol

Eleven studies (2942 participants, 5109 attacks) have compared paracetamol 1000 mg, alone or in combination with an antiemetic, with placebo or other active comparators such as sumatriptan 100 mg. For all efficacy outcomes paracetamol was superior to placebo, when medication was taken for moderate-to-severe pain. Paracetamol 1000 mg plus metoclopramide 10 mg was not significantly different from oral sumatriptan 100 mg for 2-hour headache relief, but there were no 2-hour pain-free data. Adverse event rates were similar between paracetamol and placebo.

The NNT of 12 for pain-free response at 2 hours is inferior to all other commonly used analgesics. Given the low cost and wide availability of paracetamol, it may be a useful first-choice drug for acute

Table 14.3 More common non-specific drugs used as acute/abortive treatment in migraine attacks

Drug	Dose	Route of administration	Advantages	Disadvantages
NSAIDs	Higher than usually used for other types of pain • ASA: 1 g • Ibuprofen: 800–1200 mg • Dexketoprofen: 50 mg • Naproxen 1000 mg • Ketoprofen 75 mg • Ketorolac oral 20 mg or intramuscular 60 mg Indomethacin 50 mg	Oral, rectal, intravenous, intranasal	Can be combined with triptans to achieve better efficacy Relief of pain and associated symptoms	Usually not useful for severe attacks
Acetaminophen/ paracetamol	1 g	Oral, intravenous	Can be combined with antiemetics (as metoclopramide), increasing considerably its efficacy (in some studies—similar to sumatriptan)	Generally does not work with moderate-to-severe attacks

NSAIDs, non-steroidal anti-inflammatory drugs; ASA, acetylsalicylic acid.

migraine in those with contraindications to, or who cannot tolerate, NSAIDs or aspirin (90).

Other NSAIDs such as dexketoprofen trometamol (91), and other analgesics such as metamizol, bearing in mind the risk of agranulocytosis (92), have shown efficacy in the treatment of acute migraine. Other routes of administration, such as nasal spray, have been tried with good results (93). Recommending one analgesic over another can be difficult because the data that compare these compounds are insufficient; the published clinical trials do not reflect clinical practice particularly well and low doses are probably used. The only clear recommendation in this group of compounds is for paracetamol as a first-choice drug for migraine attacks during pregnancy, and possibly ASA in patients with cardio- and cerebrovascular comorbidities.

Combination analgesics

Different combinations have been tested, with the association of ASA, paracetamol and caffeine showing a significant efficacy on migraine attacks of moderate intensity and moderate disability (94). Indomethacin, prochlorperazine, propyphenazone, and codeine have also been tested with positive outcomes. Theoretically, the combinations have the same indications of simple analgesics and NSAIDs. These combinations are not recommended as first-line therapy because the use of caffeine or codeine could increase the risk of medication overuse (10,13,14).

Dopamine antagonists

Dopamine antagonists have an established role in the treatment of migraine. Neuroleptics/antiemetics, which antagonize the dopamine D2 receptor, have variable activity as α-adrenergic blockers, antiserotonergics, anticholinergics, and antihistaminergics. Their dopamine-related action is the reason for their efficacy in treating acute migraine and nausea. Antiemetics should be given not only to patients who are vomiting or likely to vomit, but also to those with nausea, which is one of the most disabling symptoms (15). Metoclopramide is recommended as an adjunct in the treatment of nausea associated with migraine, usually in the form of tablets (10 mg); a spray and injectable form (10–20 mg) are also available for the most severe cases. There is also some evidence for the efficacy of domperidone.

Theoretically, owing to the suspected gastric stasis during the migraine attack, the association of an antiemetic with analgesics, NSAIDs, or even triptans could increase the absorption and the efficacy of the symptomatic drug; however, in clinical trials the evidence for this combination is low.

Metoclopramide, prochlorperazine and chlorpromazine have also shown a modest antimigraine effect, besides a clear antiemetic effect (95). Dopamine antagonists are an effective option in patients who have contraindications for migraine-specific medications or NSAIDs, or in pregnant women with migraine (15).

Dopamine antagonists are first-line agents in the emergency room setting, especially for acute migraine patients with nausea and vomiting. Neuroleptic medications are commonly used in status migrainosus or medication overuse headache. Nevertheless, they should be used with caution in order to avoid adverse events such as sedation, akathisia, dystonic reactions, neuroleptic malignant syndrome, or movement disorders (usually appearing after long-term use). Some of the newer atypical neuroleptic agents are promising for both acute and prophylactic migraine treatment with a lower risk of adverse events (95). Diphenhydramine may be co-administered to avoid the many extrapyramidal adverse effects of antidopaminergic drugs.

The IV form of metoclopramide (96,97), chlorpromazine, and prochlorperazine are used effectively in emergency department settings.

Barbiturate hypnotics

Barbiturate hypnotics (butalbital) lead to overuse, dependence, and withdrawal effects, and may not offer additional pain relief to justify their use. Their use has to be monitored and limited. They are not recommended as a first-line therapy for the acute treatment of migraine (10–14).

Opioids

Oral opioids and opioid combination products may relieve acute migraine pain, but there is a high risk of overuse and dependency. The association of codeine has demonstrated an increase of the efficacy of paracetamol in some studies (98), but not in others (99).

Butorphanol tartrate is a potent synthetic mixed agonist–antagonist, and administered as nasal spray it has been effective against placebo (100), but there are no studies comparing butorphanol with other non-opioid symptomatic antimigraine drugs.

Tramadol combined with acetaminophen has shown efficacy in a trial against placebo (101), but it had the same risk of dependence and abuse as the other compounds of this group.

For the listed reasons, oral opioids, including codeine, are not recommended for routine use in migraine (102). Codeine-containing combination analgesics may be considered for patients with migraine in case of triptans and/or NSAID failure or contraindication.

Home rescue in acute migraine

In patients with severe attacks treatment with triptans, alone or in combination with NSAIDs, can fail on some occasions and it is important to discuss with the patient a rescue medication strategy. There are several alternatives.

Oral NSAIDs are unlikely to provide adequate pain relief. Ketorolac IM (the patient should be carefully trained) has provided good results in an open study (103). If the patient is vomiting, the use of suppositories could be considered. Indomethacin suppositories in combination with prochlorperazine and caffeine provide a high pain-free score at 2 hours (104). The combination of indomethacin and prochlorperazine could be an alternative. Prochlorperazine suppositories (at a dose of 25 mg) have been efficacious in pain relief in a small trial (105).

Short-term high-dose steroid treatment has a place in the treatment of status migrainosus, although there is a lack of randomized clinical trials (106). By extension, a short course of prednisone or dexamethasone starting with a high dose and tapering down in 2–3 days' time might be helpful in a refractory attack. The evidence for the efficacy of corticosteroids alone is very low; only dexamethasone has shown some efficacy in a trial in menstrual-related migraine (107). The frequency of use should be limited to once a month or less.

Opioids and opioid-containing combination analgesics are not recommended for routine use in migraine, but they could be an alternative in some refractory attacks. Strong opioids such as morphine

should be avoided and used only in exceptional circumstances. The frequency of use of all compounds should be carefully monitored and limited to avoid medication overuse headache, abuse, dependence, and possible addiction.

DHE applied as a nasal spray (2 mg) or as a SC or IM injection (1 mg) is an option but only in patients who have not taken triptans.

Hospital rescue in acute migraine

Considering hospital rescue medication in acute migraine, the choice of the treatment should be based on efficacy, side effects, and cost. Headache recurs in more than 50% of patients after emergency department discharge. Parenteral opioids, NSAIDs, sumatriptan, neuroleptics, and steroids have all demonstrated some effectiveness in acute migraine treatment (108–110).

Opiates/opioids generally are not recommended as first-line treatment. Meperidine, tramadol, and nalbuphine are most commonly used. They were all superior to placebo in relieving migraine pain but not superior to other medications such as DHE or prochlorperazine. They can be effective sometimes, but such rescue therapy may lead to early headache recurrence, central sensitization, sedation, nausea, and dizziness, as well as overuse and abuse. Although, these medications are commonly administered for treatment of acute migraine, they should be a last resort (110,111).

NSAIDs (ketorolac IV and IM is the most studied) (112) are well tolerated, and they may provide benefit even when given late in the migraine attack. Ketorolac is appropriate for patients with vascular risk factors and it does not cause sedation. NSAIDs can be combined with most other treatments to increase their efficacy. Lysine clonixinate and metamizol (non-NSAID) IV have been superior to placebo in small studies (113). Dexketoprofen IV was also efficacious in the treatment of acute migraine and similar to IV paracetamol in a randomized trial (113).

Parenteral administered dopamine antagonists are not only effective antiemetics, but also can reduce or terminate migraine attacks and are recommended as first-line agents (114). Dopamine antagonists can be given alone or with other agents. They are effective, even if they are applied late in the migraine attack. They are not expensive, but they frequently cause sedation, and in some cases akathisia and dystonia that can prolong patients' functional disability.

Sumatriptan SC is as effective as droperidol and prochlorperazine. When patients have no contraindications, it is very well tolerated. Sumatriptan was inferior or equivalent to the neuroleptics and equivalent to DHE.

Corticosteroids (dexamethasone and prednisone) are superior to placebo and may prevent headache recurrence after discharge (115,116), especially if the presenting migraine has lasted longer than 72 hours. IV doses in the emergency department are usually followed by oral dosing for several days postdischarge.

IV sodium valproate has shown good results in acute or prolonged migraine headache (117), although in a recent trial it was inferior to metoclopramide or ketorolac (118). The role of new IV antiepileptics such as lacosamide or levetiracetam is not yet established.

Magnesium IV can be an effective treatment when aura is present. It can reduce the photophobia and phonophobia. Magnesium can be added on to any medication. Magnesium also can be useful for pregnancy-associated migraine, although a recent meta-analysis has failed to demonstrate a beneficial effect of magnesium in acute migraine (119) and is not recommended in the guidelines (114,116).

The following list shows the average percentage of pain relief obtained for all medications for which there were two or more randomized trials: droperidol 82%; sumatriptan 78%; prochlorperazine 77%; tramadol 76%; metamizole 75%; metoclopramide IV 70%; DHE 67%; chlorpromazine 65%; ketorolac 30 mg IV 60%; meperidine 58%; metoclopramide IM 45%; magnesium 43%; ketorolac 60 mg IM 37%; and valproate 32% (110).

Analysis of a large number of studies confirms that a definitive and optimally effective migraine rescue regimen cannot be determined. The ideal acute migraine rescue therapy administered in urgent settings would provide complete headache relief, possess no side effects, and prevent early headache recurrence. Because such therapy does not exist, treatment must be tailored to the needs of the individual patient.

The medications more recommended by the guidelines, based on a high or moderate level of evidence, are: prochlorperazine, metoclopramide, and sumatriptan SC (114,116). Lysine ASA and ketorolac are also recommended based on a moderate-to-low level of evidence (114). The guidelines also recommend avoidance of the use of opioids; the use of opioids could be associated with a long stay in the emergency department and higher rates of return (120).

Intravenous treatment in status migrainosus

Status migrainosus refers to severe migraine episodes that last more than 72 hours (8), usually accompanied by severe nausea and vomiting, which can impede oral administration of drugs. Many patients may require hospital admission to achieve an optimal management.

The treatment principles for status migrainosus include the following: (i) fluid and electrolyte replacement (if indicated); (ii) parenteral pharmacotherapy to control pain; and (iii) treatment of associated symptoms of nausea and vomiting. In these cases, the IV route, which eliminates the need of absorption and yields a quicker drug effect (121), can be used for correction of fluid and electrolyte imbalances and treating pain. For relieving nausea and vomiting, IV metoclopramide, chlorpromazine, or prochlorperazine can be used. Intravenous or IM metoclopramide has shown a good efficacy for the acute treatment of migraine. There are few studies suggesting that chlorpromazine IV has a therapeutic role in the acute treatment of migraine in the emergency settings. Metoclopramide, prochlorperazine, and chlorpromazine all can cause drowsiness or sedation. Acute dystonic reactions and akathisia are rare (32).

Neuroleptics may be useful because of their sedative and antiemetic action (e.g. 100 mg IV tiapride dissolved in dextrose).

IV corticosteroids (4–8 mg of dexamethasone every 6–8 hours or 20–40 mg of prednisolone every 6–8 hours, with a subsequent tapering dose for 3–4 days) are also effective in controlling headache and accompanying symptoms (122). Analgesics and NSAIDs have a minor role in these cases, but may be helpful as adjuvant therapy when combined. Non-oral triptans, such as 6 mg SC sumatriptan, 10–20 mg intranasal sumatriptan, or 5 mg intranasal zolmitriptan, could be an initial treatment of choice in status migrainosus if the patient has not used triptans or ergotamine for the treatment of the attack (15).

IV DHE (0.5 mg) combined with IV antiemetics is also an effective option. It can be administered every 8 hours if there is no headache relief (13,15). The peak concentration toxicity should be considered while using IV administration. It can be mitigated by using brief infusions lasting 20–30 minutes (15).

Future treatments

Calcitonin gene-related peptide antagonists

Since the triptans were introduced in the 1990s, the calcitonin gene-related peptide (CGRP) blockers are the only new specific drugs developed for acute migraine treatment with an extensive programme of clinical trials. Their mechanism of action is based on the pathophysiology of the disease (123). Clinical trials have proved that CGRP receptor antagonists/gepants are effective for treating migraine, and antibodies to the receptor and CGRP are currently under investigation as a preventive treatment. (124) (see Chapter 15). The first evidence of CGRP receptor blockade in migraine using IV olcegepant was published in 2004 (125). Later studies have been done with the orally administered telcagepant (126,127). CGRP receptor blockers inhibit CGRP-induced vasodilatation and they do not seem to exert an effect on coronary arteries, and cardiovascular parameters, and, unlike triptans, they might be a possible option for migraine patients with coronary disease (128). Telcagepant showed liver toxicity in a prophylactic trial and the programme was stopped. Recently, ubrogepant has shown some positive results against placebo (129). GCRP antagonists are superior to placebo, but not superior to 5-HT_1 agonists in the usual indices used in clinical trials (130).

Neuromodulation

Neuromodulation is an alternative method for treatment and modifies pain signals through reversible modification of the function of the nociceptive system by exogenous electrical currents application (131). These techniques are especially used in the preventive treatment of refractory patients, but some of them have also been used as acute treatment (see Chapter 16).

Transcranial magnetic stimulation (TMS) is thought to disrupt cortical spreading depression by delivering a fluctuating magnetic field from the scalp by which small electrical currents are induced in the brain (132). The single-pulse TMS increased freedom from pain at 2 hours versus sham stimulation in patients with migraine with aura (133). An open postmarketed study has demonstrated some efficacy in acute and chronic migraine, with good tolerability (134).

Vagus nerve stimulation (VNS) is a procedure available for resistant epilepsy (135), and it has been recently approved by the FDA as an adjunctive treatment in chronic or recurrent medication-resistant depression (136). In retrospective studies, VNS has been shown to improve episodic migraine (137). A small portable device (gammaCore) has been developed for acute and prophylactic treatment for migraine and cluster headache. Some positive results have been published in open studies of the acute treatment of migraine (138), and an extensive programme of clinical trials is running to explore its utility in acute and preventive migraine treatment.

Conclusion

Treatment management and strategies for acute migraine are not unified. Certain guidelines and the 'stratified care' principles only assist in choosing the best treatment for patients with this troublesome disorder. This literature review focuses on the clinical efficacy and tolerability of the most commonly used drugs for acute migraine treatment, together with their various routes of administration. Descriptions of advantages, disadvantages, and recommended dosages are based on human studies and clinical practice. Nevertheless, the individual approach to every patient has to be the key principle in acute migraine management. Treatment strategy should be based on migraine clinical characteristics: severity of the attack, time for peak intensity to be reached, frequency of attacks, severity of other associated symptoms, co-existing conditions and illnesses, other medications/interactions, and prior migraine therapy response (73).

Patients should be educated to recognize the beginning of their attack and to take their medication as soon as possible, before the occurrence of allodynia, which can possibly attenuate the length of the attack. The best route of drug administration should be chosen, based on the presented symptoms during an attack and the patient's needs (139,140). If some of the medications fail, the clinician has to make sure that at least two attacks have been treated before deciding that it is ineffective. Clinicians have to ensure that the dose is adequate and that there are no other factors interfering with the drug's effects.

A self-administered rescue medication is needed when other treatments fail to work. Although they may not eliminate pain completely or return patients to their normal functioning, they provide a certain relief without visiting the physician's office or the emergency department (13).

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15

Treatment and management of migraine

Preventive

Andrew Charles and Stefan Evers

Introduction

A significant percentage of individuals with migraine, by some estimates as many as 25%, are candidates for preventive therapy, also known as prophylactic therapy (1). These are treatments that are administered to pre-empt headache attacks, as opposed to acute treatments that are administered once a headache attack has occurred (although many treatments may be effective both as preventive and acute therapies). There are a variety of options for preventive therapy with widely varying mechanisms of action, and there is no clear-cut single choice for any individual patient. Preventive therapies can be broadly grouped as antihypertensive medications, anticonvulsant medications, antidepressants, vitamins, natural therapies, neurotoxins, and neuromodulation approaches. Early clinical trials indicate that antibody therapies may play an important role as future migraine preventive therapies. While current therapies are effective for some patients, there is a critical need for better means of identifying which strategy is the best for each individual patient, and also for new approaches that are more effective and better tolerated for the prevention of migraine overall.

Indications for preventive therapy

The decision to begin preventive therapy should be individualized based on a number of factors including:

- frequency and duration of attacks;
- level of disability caused by attacks;
- efficacy of acute therapy;
- co-morbid conditions;
- tolerability of the preventive therapy being considered;
- severely disabling migraine aura;
- lifestyle adjustments, changes in current medications (particularly addressing acute medication overuse), or behavioural approaches that could be considered before instituting preventive therapy.

Guidelines recommend that preventive medications should be considered if more than 2–3 migraine attacks occur per month, if acute therapy is ineffective, or to try to prevent acute medication overuse. Other potential indications for preventive therapy include the occurrence of particularly disabling attacks, even if infrequent, or the occurrence of severe or disabling aura, given that aura does not respond to any currently available acute medications.

Because preventive therapies are by their nature designed to have a sustained duration of action, they are also likely to have more sustained and long-term side effects than acute medications. An interesting unanswered question is whether migraine preventive therapy has any effect on the progression of the disorder. Some have hypothesized that early use of migraine preventive therapy could reduce progression from an episodic to a chronic condition (2). One study with topiramate, however, found that it did not prevent progression of migraine despite clear efficacy versus placebo (3), and there is no long-term longitudinal evidence to support the hypothesis that preventive therapy protects against progression. Better longitudinal studies of different preventive therapies are essential in order to determine the long-term effects of migraine preventive therapy.

Assessing efficacy/tolerability of therapy

As with the decision to initiate preventive therapy, the assessment of the efficacy of therapy is highly individualized. Parameters that indicate efficacy and tolerability include:

- frequency and duration of attacks;
- severity of attacks;
- acute medication use and efficacy of acute medications;
- adverse effects;
- overall function/disability.

Each of these parameters may carry different weight for different individuals. In clinical trials of preventive therapies, the percentage of patients showing a 50% reduction in headache days is a commonly used parameter by which efficacy of therapy is determined. Given the clinical heterogeneity of migraine and the likelihood that multiple distinct pathophysiological mechanisms exist

in different individuals, it may also be useful to examine subgroups of responders, i.e. those with 100% reduction in headache, 75% reduction, and so on. This may help to identify subgroups of patients for whom a given therapy is particularly effective. Quality-of-life measures and disability measures may also be highly useful, because they consider both efficacy of medications and adverse effects. Acute medication use is also an important indicator of the efficacy of therapy.

Duration of therapy

The duration of therapy that constitutes a 'fair trial' of a medication varies based on a number of factors. Most clinical trials of migraine preventive therapy have a duration of at least 3 months, and this amount of time is commonly considered to be a minimum duration of therapy to evaluate efficacy. Obviously, this minimum duration may be reduced if the medication is poorly tolerated. A more controversial issue is how long therapy should be continued if it *is* effective. Some evidence indicates that patients may continue to have decreased headache frequency and severity for an extended period after preventive therapy is stopped (4). These studies raise the possibility that even when a therapy is effective, it may be advisable to use preventive therapy for months rather than years at a time

Identification of migraine preventive therapies

None of the migraine preventive therapies in current widespread use was initially indicated for migraine, and until recently very few therapies were developed specifically to treat the disorder. Some of the earliest identified migraine preventive therapies, particularly beta blockers, were hypothesized to work by 'stabilizing' blood vessels, a hypothesis that has been challenged by substantial evidence that migraine is not primarily caused by changes in vascular calibre (5,6). Other therapies, such as tricyclic antidepressants, were believed to work by modulating levels of serotonin and norepinephrine. More recently, there has been in increased focus on the possibility that migraine preventive therapies may work by reducing brain excitability similar to that underlying seizures. This idea has led to the use of anticonvulsants, such as valproic acid and topiramate, as migraine preventive therapies. In animal models, the ability to suppress cortical spreading depression (CSD; the slowly propagated wave of cortical activity that may underlie the migraine aura) may have some value as a predictor of the efficacy of migraine preventive therapy (7). However, not all medications that prevent migraine inhibit CSD, and some medications that do not prevent migraine do inhibit CSD (8). The development of new translational models that can reliably identify migraine therapies would represent a valuable step toward.

Choice of preventive therapy

The choice of a preventive therapy for any given migraine patient requires consideration of multiple factors, and may not be straightforward. Among the guidelines that have been generated by different organizations to help clinicians and patients make decisions regarding migraine preventive therapy, there are at least 30 different choices within the top-three tiers of recommendations (Table 15.1) (9–12).

The existence of such a wide array of choices of preventive medications for migraine, with diverse mechanisms of actions, underscores the fact that there is no single medication or class of medications that is consistently effective and well tolerated for the majority of patients with the disorder. Nonetheless, as indicated by the guidelines, there are a number of choices that are more consistently recommended than others. In many cases, the choice of a migraine preventive therapy is based on an individual patient's comorbidities, rather than by a definitively superior efficacy of one therapy over another. The features of medications among the top choices for migraine prevention are outlined in the following sections.

Antihypertensive medications

Beta adrenergic blockers

Several beta adrenergic blockers have been sufficiently studied in clinical trials and used extensively in clinical practical such that they can be recommended as migraine preventive therapy. These include propranolol, metoprolol, nadolol, timolol, atenolol, and bisoprolol. Beta blockers inhibit the action of the endogenous catecholamines epinephrine (adrenaline) and norepinephrine (noradrenaline), on β-adrenergic receptors. Beta blockers are believed to work primarily on two types of β-adrenergic receptor, namely the β1 and β2 receptors (13). Both subtypes are present in the brain. β1-adrenergic receptors are also located primarily in the heart and kidneys, whereas β2-adrenergic receptors are located in other tissues, including smooth muscle, skeletal muscle, lungs, gastrointestinal tract, and liver. Of the medications listed, propranolol, nadolol, and timolol are non-selective beta blockers, whereas metoprolol, atenolol, and bisoprolol are relatively selective B1 blockers. Atenolol and nadolol have low lipid solubility, which may be correlated with reduced blood–brain barrier penetration. Bisoprolol has low-to-medium lipid solubility; metoprolol and timolol have medium lipid solubility; and propranolol has high lipid solubility (13). Given the fact that a broad range of beta blockers is efficacious in migraine prevention, the receptor specificity and lipophilicity of beta blockers seem not to play a role in their antimigraine action.

The mechanism(s) of action by which beta blockers exert their therapeutic effects in migraine prevention are not known. In one study, propranolol and metoprolol were found to reduce the amplitude of visual evoked potentials in patients with migraine, although this change was not necessarily correlated with the efficacy of these medications as migraine preventive therapy (14). In another study, treatment with either metoprolol or bisoprolol reduced the intensity dependence of the auditory evoked cortical potentials, an effect that was correlated with clinical improvement (15). In rodent models, propranolol has been shown to inhibit CSD (16). Taken together, these results suggest that at least one mechanism of action of beta blockers may be the modulation of brain excitability.

Propranolol is the most widely studied of the beta blockers. More than 20 placebo-controlled trials showed significantly greater efficacy of propranolol compared with placebo for migraine prevention, and a meta-analysis of studies of propranolol at any dose including more than 600 patients showed a significantly greater 50% responder rate and significant reduction in headache days (17). Studies comparing the efficacy of propranolol with metoprolol, flunarizine,

Table 15.1 Guidelines for the preventive treatment of episodic migraine.

AHS/AAN	Canadian Headache Society	EFNS
Level A: established as effective; should be offered Divalproex/sodium valproate 400–1000 mg/day Metoprolol 47.5–200 mg/day *Petasites* (butterbur) 50–75 mg q12h Propranolol 120–240 mg/day Timolol 10–15 mg q12h Topiramate 25–200 mg/day	**Strong recommendation (level of evidence)** Amitriptyline (high) Candesartan (moderate*) Coenzyme Q10 (low) Gabapentin (moderate) Magnesium (low) Metoprolol (high) Nadolol 80–160 mg/day (moderate) *Petasites* (moderate) Propranolol (high) Riboflavin 400 mg/day (low) Topiramate (high)	**Drugs of first choice** Flunarizine Metoprolol Propranolol Topiramate Valproic acid
Level B: probably effective; should be considered Amitriptyline 25–150 mg/day Atenolol 100 mg/day Fenoprofen 200–600 mg q8h Feverfew 50–300 mg q12h; 2.08–18.75 mg q8h for MIG-99 Histamine 1–10 ng SC twice weekly Ibuprofen 200 mg q12h Ketoprofen 50 mg q8h Magnesium 600 mg/day Naproxen 500–1100 mg/day Naproxen sodium 550 mg q12h Riboflavin 400 mg/day Venlafaxine ER 150 mg/day	**Weak recommendation** Divalproex/sodium valproate (high) Flunarizine 10 mg/day (high) Lisinopril (low) Pizotifen 1.5–4 mg/day (high Venlafaxine (low) Verapamil (low)	**Drugs of second choice** Amitriptyline Bisoprolol 5–10 mg Naproxen *Petasites* Venlafaxine
Level C: Possibly effective; may be considered Candesartan 16 mg/day* Carbamazepine 600 mg/day Clonidine 0.75–0.15 mg/day Guanfacine 0.5–1 mg/day Lisinopril 10–20 mg/day Nebivolol 5 mg/day Pindolol 10 mg/day Flurbiprofen 200 mg/day Mefenamic acid 500 mg q8h Coenzyme Q10,100 mg q8h Cyproheptadine 4 mg/day		**Drugs of third choice** Acetylsalicylic acid 300 mg Gabapentin Magnesium *Tanacetum parthenium* 3–6.25 mg Riboflavin Coenzyme Q10 Candesartan Lisinopril Methysergide 4–12 mg
Possibly/probably ineffective; should not be offered Acebutolol Clomipramine Clonazepam Lamotrigine Montelukast Nabumetone Oxcarbazepine Telmisartan	**Recommendation against** Feverfew (high) Botulinum toxin	

AHS, American Headache Society; AAN, American Academy of Neurology; EFNS, European Federation of Neurological Societies; SC, subcutaneous.

*Note that an additional study that strengthens evidence for candesartan has been published since these guidelines were developed. Also, importantly, these guidelines did not include studies of monoclonal antibodies targeting calcitonin gene-related peptide for migraine prevention.

Source data from: Silberstein SD, Holland S, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1337–45; Evers S, Afra J, Frese A, Goadsby PJ, Linde M, May A, et al. EFNS guideline on the drug treatment of migraine—revised report of an EFNS task force. *Eur J Neurol*. 2009;16:968–81; Pringsheim T, Davenport W, Mackie G, Worthington I, Aube M, Christie SN, et al. Canadian Headache Society guideline for migraine prophylaxis. *The Canadian journal of neurological sciences*. 2012;39:S1–59; Holland S, Silberstein SD, Freitag F, Dodick DW, Argoff C, Ashman E. Evidence-based guideline update: NSAIDs and other complementary treatments for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78:1346–53.

amitriptyline, and candesartan showed comparable benefit for migraine prevention, whereas one study showed superiority of nadolol over propranolol (18). In clinical trials, propranolol was generally well tolerated with less than 5% drop-out due to adverse events. Common adverse effects include fatigue, reduction in heart rate, reduction in blood pressure, and sexual dysfunction (13,17,19). Common contraindications to use of a beta blocker include insulin-dependent diabetes mellitus and asthma. Beta blockers, particularly those with higher lipid solubility, may have the potential to worsen depression, although this effect has not been confirmed in a number of studies (19,20). Other relative contraindications to the use of beta blocker for migraine prevention include glaucoma and prostatic hypertrophy.

Practical considerations

There is strong evidence for the efficacy of beta blockers as migraine preventive therapies. They may be a good first choice for individuals who have hypertension or who have tachycardia at baseline. It remains unclear whether the more lipid soluble and therefore more centrally acting beta blockers have any advantage over those that are less lipid soluble. It is also not clear whether there is a significant difference between β1 selective blockers and non-selective blockers of β1 and β2 receptors. Recent analyses suggest that there may be increased stroke risk associated with non-selective beta blockers versus with β1 selective blockers, possibly related to increased variability of blood pressure with the non-selective blockers (21). Non-selective blockers may therefore be contraindicated in older individuals or those at increased risk of stroke

Candesartan

Mechanism of action

Candesartan is administered as a prodrug, candesartan cilexetil, that is metabolized to candesartan during absorption from the gastrointestinal tract (22). Candesartan selectively blocks the AT_1 subtype of the angiotensin II receptor. $AT(_1)$ receptors are located primarily in vascular smooth muscle and adrenal glands, and by activation of these receptors, angiotensin II has a variety of effects, including contraction of vascular smooth muscle, release of adrenal catecholamines, augmentation of noradrenergic neurotransmission, and an increase in sympathetic tone (22). AT_1 receptors are also located in the brain and spinal cord, where they have been reported to modulate pain transmission (23,24).

Clinical trial evidence

A crossover study comparing candesartan 16 mg to placebo found a significant reduction in the number of days with headache or migraine during active treatment compared with the placebo period, as well as a significant difference in 50% responder rate (25). A more recent study comparing candesartan with propranolol and placebo found that the efficacy of candesartan was similar to that of

propranolol based on reduction in headache days and responder rate, and both were superior to placebo (26). Candesartan was generally well tolerated, although dizziness and paraesthesias occurred more commonly with candesartan than with propranolol. Interestingly, telmisartan, another $AT_{(1)}$ receptor antagonist, was not efficacious in migraine prevention.

Practical considerations

Candesartan is generally well tolerated. A trial of candesartan is particularly worth considering in patients with hypertension in addition to migraine, or those who have found other migraine preventive approaches difficult to tolerate. It should not be used during pregnancy because of risk of fetal toxicity (category D).

Antidepressants

Amitriptyline

Mechanisms of action

Multiple tricyclic antidepressants are commonly used as migraine preventive therapies (27), but the only one with established efficacy is amitriptyline. Amitriptyline inhibits the transporters for serotonin and, to a lesser extent, norepinephrine, which is responsible for uptake of these neurotransmitters from the synaptic cleft (28,29). It is metabolized to nortriptyline, which also inhibits serotonin and norepinephrine uptake but is a more potent inhibitor of norepinephrine uptake. Amitriptyline also has a variety of other mechanisms of action that may be relevant to migraine. It inhibits sodium, calcium, and potassium channels, and also acts as an antagonist at serotonin receptors, histamine receptors, and muscarinic acetylcholine receptors (28,29). Amitriptyline's inhibition of serotonin and norepinephrine uptake are not correlated with its efficacy as a migraine preventive therapy, as other more potent uptake inhibitors do not clearly have greater efficacy for prevention of migraine. The antidepressant effects of amitriptyline are also not correlated with its migraine preventive effects (30).

Clinical trial evidence

Amitriptyline has not been as extensively studied in clinical trials as other migraine preventive therapies, and the quality of the studies done has not been as high as that for other therapies (11,30). Amitriptyline had better efficacy than placebo in four placebo controlled trials in adults (31–34). Its efficacy was the same as propranolol and fluvoxamine in two trials (33,34). The quality of these studies was not high, and in two of the placebo-controlled trials, the end points make the results difficult to compare with other preventive therapy studies. In the other two placebo controlled trials, however, amitriptyline reduced attack frequency by 42% and by up to 51% versus placebo. In the latter trial, amitriptyline appeared to be superior to propranolol because it improved all efficacy parameters, whereas propranolol improved only a severity and headache score. Two recent trials compared amitriptyline to topiramate without placebo control (35,36). Both showed no significant difference in efficacy between topiramate and amitriptyline. Another recent study of young people aged 10–17 years found that amitriptyline plus cognitive behavioural therapy resulted in a substantially greater responder rate and reduction of headache days versus amitriptyline combined with headache education (37).

The doses of amitriptyline used varied considerably in clinical trials, ranging from 10mg to 150 mg. Common adverse effects of amitriptyline in clinical trials included drowsiness (the most common adverse effect), dry mouth, weight gain, skin reactions, orthostatic hypotension, nausea, and constipation.

Practical considerations

While classified as an antidepressant, the doses of amitriptyline used for migraine are typically substantially lower than those used for depression. Also, as mentioned earlier, migraine preventive effects are not correlated with antidepressant effects. Thus, unlike other medications discussed here such as venlafaxine, amitriptyline is not necessarily a medication that can be recommended to treat depression in addition to preventing migraine. Amitriptyline is also commonly used to treat insomnia, fibromyalgia, and irritable bowel disorder. It is worth considering as a migraine preventive therapy in patients with these conditions. Nortriptyline is commonly prescribed as an alternative to amitriptyline with potentially better tolerability. This use of nortriptyline is supported by clinical experience but not by clinical trial data.

Contraindications to the use of amitriptyline include narrow-angle glaucoma, urinary retention, pregnancy, breastfeeding, and concomitant use of monoamine oxidase inhibitors. It should be used with caution in patients with kidney, liver, cardiovascular, and thyroid disease.

Venlafaxine

Mechanisms of action

Venlafaxine is a serotonin–norepinephrine reuptake inhibitor that, at low doses (< 150 mg/day), primarily inhibits the serotonin transporter, whereas at higher doses it also inhibits norepinephrine (> 150 mg/day) and dopamine (> 300 mg/day) transport (38,39). It has other effects, including modulation of opioid receptors and α2-adrenergic receptors.

Clinical trial evidence

Two trials have evaluated venlafaxine as preventive therapy for migraine. Neither is considered to be a high0quality study. One study compared venlafaxine to placebo (40), whereas another evaluated venlafaxine versus amitriptyline (41). In the first study, patients who received venlafaxine 150 mg daily had a significantly greater reduction in the median number of days with headache compared with placebo. Adverse effects, primarily nausea, vomiting, and drowsiness, caused six of 41 venlafaxine-treated patients to discontinue therapy. The trial comparing venlafaxine to amitriptyline found that venlafaxine was equivalent in efficacy to amitriptyline 75 mg daily.

Practical issues

Unlike amitriptyline, venlafaxine has antidepressant effects at doses typically used to prevent migraine, so is worth considering in patients with comorbid depression. The sustained release preparation of venlafaxine may be associated with reduced nausea, a relatively common adverse side effect of the medication. Discontinuation of venlafaxine, even missing individual doses, may result in significant withdrawal symptoms. It must therefore be tapered very slowly when therapy is discontinued.

Anticonvulsants

Valproic acid (divalproex sodium/sodium valproate)

Valproic acid is a liquid at room temperature, but the salt sodium valproate is a solid. Divalproex sodium is a mixture of the acid and the salt (42). Valproic acid has diverse mechanisms of action that

may be relevant to migraine. Among other effects, it inhibits sodium channels, increases brain levels of the inhibitory transmitter γ-aminobutyric acid (GABA), and inhibits histone deacetylases, a class of enzymes that are involved in expression of DNA (43).

Clinical trial evidence

There have been three parallel group trials and two crossover studies comparing divalproex sodium with placebo. The parallel group studies included more than 500 participants, and showed that divalproex sodium resulted in a significantly increase responder rate and a significantly lower number of migraine attacks compared with placebo (42,44–47). Adverse effects, particularly nausea, somnolence, tremor, and dizziness, were consistently higher in the divalproex sodium treatment group than in controls. In one study, 27% of patients taking the 1500-mg dose dropped out because of adverse effects.

Practical considerations

There is good-quality evidence to support the use of valproic acid, particularly in the form of divalproex sodium, as a migraine preventive therapy. However, the common occurrence of highly significant adverse effects (including those described in the previous subsection, as well as weight gain) limits more extensive use of this therapy. In addition, it has established teratogenic effects in pregnancy (category X), further limiting its potential use in women of childbearing age.

Topiramate

Mechanisms of action

Topiramate has several mechanisms of action that may be relevant to migraine. It blocks voltage-dependent sodium channels, it enhances neurotransmission mediated by the inhibitory transmitter GABA, it inhibits the action of the excitatory transmitter glutamate, the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate subtype of the glutamate receptor, and it inhibits carbonic anhydrase (48).

Clinical trial evidence

Several large parallel group trials, with varying quality, compared topiramate to placebo for migraine prevention. Topiramate 50 mg, 100 mg, and 200 mg doses have been studied, and at each dose the 50% responder rate was significantly higher compared with placebo, with the best response seen with the 100 mg dose (49). Adverse effects were common in the topiramate-treated groups, particularly with the 200-mg dose, leading to significant drop-out rates. The most commonly reported side effects were paraesthesias, weight loss, altered taste, anorexia, fatigue, and memory impairment. One of these studies also had an arm comparing topiramate 100 mg with propranolol 160 mg, which showed similar migraine frequency reduction, responder rate, and reduction in migraine days (50) . One crossover study compared topiramate to sodium valproate, finding no difference in efficacy between treatments (51). Another compared topiramate 50 mg to placebo and lamotrigine, finding that topiramate had a significantly greater responder rate compared with the placebo or lamotrigine treatment phases (52). A large parallel group study comparing topiramate 100 mg with amitriptyline 100 mg (or maximum tolerated dose) found that there was no significant difference in the efficacy of topiramate compared with amitriptyline (35). Although there was no significant difference in discontinuation due to adverse effects in either group, participants receiving topiramate had significant weight loss compared with a significant weight gain in those on amitriptyline. A large study designed to determine whether treatment with topiramate versus placebo could reduce progression from high-frequency migraine to chronic migraine found that topiramate resulted in significant improvement in headache frequency compared with placebo but did not have any effect on progression of migraine (3) .

Practical considerations

Topiramate can cause weight loss, and, in fact, was recently approved by the US Food and Drug Administration (FDA) for use in combination with phentermine for weight loss. It may therefore be appropriate to consider the use of topiramate for migraine prevention in obese patients. Topiramate was also recently approved by the FDA as a therapy for migraine prevention in adolescents. It is also one of two treatments for which there is efficacy for chronic migraine (see 'Chronic migraine'). Side effects are common with topiramate, however, and may limit its use. Cognitive dysfunction, particularly language dysfunction, can be problematic (53), and topiramate has been reported to either exacerbate or cause depression (54,55).

Other special considerations when prescribing topiramate include its interaction with oral contraceptives (decreasing effectiveness of contraception), potential to predispose to renal calculi, and, rarely, acute angle closure glaucoma, and metabolic acidosis.

Petasites

The plants commonly referred to as butterbur are found in the daisy family Asteraceae in the genus *Petasites*.

Butterbur was reportedly used by ancient cultures as a treatment for headache, and it has been hypothesized that this effect is mediated by petasin and isopetasin, compounds found in highest concentration in the plant's roots. This is the rationale for the development of butterbur root extract as a migraine preventive therapy (56).

Mechanisms of action

The mechanism of action of butterbur root extract is unknown. Speculated mechanisms of action include anti-inflammatory effects and inhibition of voltage-gated calcium channels (57,58).

Clinical trial evidence

A small (60 patients) double-blind randomized placebo-controlled trial of a specific butterbur root extract was performed more than 20 years ago, with recent re-analysis of this data (59). This study found that 100 mg butterbur was superior to placebo in all migraine preventive parameters studied. There were no significant adverse events or changes of laboratory values observed in this study. A larger (202 patients) study of a butterbur root extract found that 75 mg but not 50 mg daily was superior to placebo during a 4-month treatment period (56). Butterbur root extract was also well tolerated in this study

Practical considerations

Components of the butterbur plant are toxic to the liver, and there have been reports of severe liver toxicity as a consequence of use of extracts of *Petasites hybridus*. The patented version of butterbur root extract that was studied as described above has not been associated with any reports of liver toxicity, possibly because the extraction

procedure involved in the production of this compound removes toxins that are present in other preparations.

Flunarizine

Mechanisms of action

Flunarizine is calcium channel blocker that may also block sodium channels, inhibit H_1 histamine receptors, and modulate dopamine uptake, among other mechanisms (60). It is a vasodilator via its actions on vascular smooth muscle, but it does not inhibit coronary calcium channels. It can cause depression and extrapyramidal symptoms in humans, clearly indicating that it has actions in the brain (61).

Clinical trial evidence

Six trials of fair-to-poor quality have compared flunarizine to placebo (62). Each found a significant decrease in migraine frequency with flunarizine 10 mg daily compared with placebo. The most common adverse effects were sedation and weight gain. Three trials have compared flunarizine to pizotifen for migraine prophylaxis, all of which reported a reduction in migraine frequency in both treatment groups, with no significant difference between groups with respect to efficacy or side effects (63–65).

Practical considerations

While evidence and clinical experience indicate flunarizine is effective in migraine prevention, its significant side effects limit its widespread use.

Naproxen

Mechanisms of action

Naproxen is a non-steroidal anti-inflammatory drug (NSAID) that has established efficacy as an acute therapy for migraine, either alone or in combination with triptans. The rationale for its use as a preventive therapy is to prevent inflammatory mechanisms that may be involved in the initiation of migraine. A primary mechanism of action is the inhibition of cyclooxygenase (COX)-1 and COX-2 enzymes, which produce prostaglandins and thromboxanes from arachidonic acid (66). Other potent inhibitors of COX, such as indomethacin, however, have been shown to be ineffective in the preventions of migraine, raising doubts about this as the primary mechanism of action of naproxen in migraine prevention. The inhibition of platelet aggregation has also been proposed as a mechanism by which naproxen could prevent migraine. However, studies with high doses of acetylsalicylic acid and dipyramidole as preventive therapy did not indicate a correlation between inhibition of platelet aggregation and migraine prevention.

Clinical trial evidence

Naproxen sodium (1100 mg daily) was found in three trials to be superior to placebo in the prevention of migraine (67–69). In one trial it was comparable to pizotifen (67), and in another trial it was comparable to propranolol (70). The effects of naproxen sodium as a 'short-term preventive therapy' for menstrual migraine have also been investigated.

In one study, naproxen sodium 1100 mg daily was shown to reduce premenstrual pain, including headache (71). In other studies, naproxen sodium 1100 mg daily taken preventively prior to and during menstruation was found to significantly reduce headache severity (70), frequency (72), or both (73) compared with placebo. Gastrointestinal symptoms were the most common side effects during NSAID treatment, including dyspepsia and diarrhoea, but their frequencies of occurrence were generally not greater than those encountered in participants who took placebo, probably because of the relatively small size of the trials.

Practical considerations

Naproxen sodium be administered with extreme caution in patients with a history of ulcer disease or gastrointestinal bleeding because of the potential risk of gastrointestinal bleeding caused by its use.

The use of NSAIDS, particularly for long durations or in individuals with risk factors, has also been associated with an increased risk of myocardial infarction and stroke (74).

Interestingly, unlike most other preventive therapies, naproxen sodium and other NSAIDS are also used as acute migraine therapies. Paradoxically, when used frequently as an acute therapy, NSAIDS are among the medications that are considered as part of the classification of medication overuse headache. At this stage it is not clear how to reconcile this classification with their use as a preventive therapy.

Vitamins and naturally occurring compounds

Riboflavin

Mechanism of action

Riboflavin is a key component of flavoproteins, which serve as cofactors in mitochondrial energy metabolism. The rationale for use of riboflavin as a preventive therapy for migraine is based on the hypothesis that deficiency in mitochondrial energy metabolism contributes to migraine, and that oral riboflavin could improve this deficiency (75). Whether or not supplemental riboflavin does improve mitochondrial energy metabolism in those with migraine is unclear.

Clinical trial evidence

One study with 55 patients found that riboflavin was superior to placebo in reducing migraine attack frequency and headache days (76). A study comparing a combination of riboflavin 400 mg in combination with magnesium and feverfew versus riboflavin 25 mg alone found no difference in migraine frequency between the two treatment groups (77). A randomized, double-blind study of riboflavin 200 mg in children showed no difference compared with placebo for end points of 50% responder rate, severity of migraine, associated symptoms, or analgesic use. Similarly, a crossover study of riboflavin 50 mg versus placebo in children showed no difference between groups for the end point of migraine attack frequency.

Practical considerations

Riboflavin is commonly recommended as migraine preventive therapy because of its exceptional tolerability and low cost, but the evidence for its efficacy is limited to a single study, whereas other studies have shown no benefit.

Coenzyme Q10

Mechanism of action

Coenzyme Q10, also known as ubiquinone, is a component of the electron transport chain in mitochondria. The rationale for its use in migraine is similar to that for riboflavin, i.e. that supplemental oral

coenzyme Q10 will increase deficient energy metabolism that has been proposed to be involved in migraine (78).

Clinical trial evidence

One open-label (79) and one randomized, double-blind, placebo-controlled study (80) evaluated the efficacy and tolerability of coenzyme Q10 100 mg given three times daily as preventive therapy for migraine in adults. In the latter study of 42 patients, treatment with coenzyme Q10 was superior to placebo for the primary end point of improvement in attack frequency after 3 months versus baseline. There was also significantly greater 50% responder rate for attack frequency in the coenzyme Q10 group (47.6%) compared with the placebo group (14.3%). No significant adverse effects were reported. A placebo-controlled, double-blind, crossover, add-on trial of 100 mg of coenzyme Q10 in 122 children and adolescents found no differences between treatment and placebo in migraine frequency, severity, or duration in last 4 weeks of treatment versus baseline (81).

Practical considerations

Like riboflavin, the evidence supporting coenzyme Q10 is as a migraine preventive therapy is weak, but it is often prescribed for migraine because of its exceptional tolerability. In the one placebo-controlled study in which it was found to be effective, a liquid preparation was used (80). Whether or not this preparation is superior to a tablet form, and whether or not there is any dose dependence of its potential efficacy, remains uncertain.

Chronic migraine

Patients with very frequent migraine represent a distinct therapeutic challenge, owingto the common occurrence of medication overuse in this patient group, the common association of other comorbidities, and possibly owing to distinct pathophysiological mechanisms that take place when attacks of headache occur very frequently (see also Chapter 31). The classification of chronic migraine (15 or more headache days per month, with eight or more of them meeting criteria for migraine) was created to acknowledge that individuals with very frequent migraine may have distinct pathophysiological mechanisms and require different therapies (82). The specific definition of chronic migraine was based in part on empirical observations of the effects of onabotulinum toxin, which did not show efficacy in clinical trials for patients in whom headache occurred on less than 15 days per month. Thus, while the designation of 15 days as a cut-off for the classification of chronic migraine has now become widely accepted, it is important to recognize that as far as preventive therapy is concerned, onabotulinum toxin is the only medication for which there is evidence to support specific therapeutic efficacy based on this classification. Other preventive therapies may also be effective in the setting of chronic migraine, although the efficacy for this indication has not been specifically studied. For example, studies of both sodium valproate (83,84) and amitriptyline (85) suggest benefit for chronic daily headache (including both chronic migraine and tension-type headache). Because of the classifications used for these studies they cannot be directly compared to those described in the following subsections; nonetheless, they raise the possibility that there may be other medications that are efficacious for chronic migraine. Multiple monoclonal antibodies targeting calcitonin gene-related peptide (CGRP) have now also been studied as therapies for chronic migraine. These are discussed separately.

Topiramate

As described earlier, topiramate was found to be effective as a preventive treatment for episodic migraine in multiple large, well-designed studies. Topiramate was initially found to be specifically effective as a therapy for chronic migraine in a small placebo-controlled trial of patients with acute medication overuse (86). This study was followed by two large, double-blind, placebo-controlled studies of the efficacy and tolerability of topiramate 100 mg for chronic migraine (87,88). Both studies met their primary end point of reduction in the number of headache days per month. In one study, patients with medication overuse were excluded, whereas in the other they were not. Although topiramate was effective as preventive therapy even in patients with medication overuse, there was not a significant reduction in the mean days of acute medication use in either study. Adverse effects were similar to those reported in studies of episodic migraine, namely paraesthesias and fatigue.

Botulinum toxin

Botulinum toxin was originally identified as a potential therapy for migraine prevention based on anecdotal reports from patients who were receiving it for cosmetic indications. Several clinical trials investigating onabotulinum toxin A injections as preventive therapy for episodic migraine did not show efficacy (89). Because post-hoc analysis of these studies indicated potential efficacy for patients with frequent headache, subsequent studies were performed with patients who had more than 15 headache days per month, and these studies led to international approval of the use of onabotulinum toxin for the prevention of chronic migraine (82).

Mechanisms of action

Botulinum toxin is taken up by cells by binding to cholinergic neurons via a synaptic vesicle protein 2 in conjunction with gangliosides (90,91). When administered in vivo, it is taken up primarily by cholinergic neurons, including motor neurons that are responsible for muscle contraction, as well as autonomic neurons that mediate sympathetic and parasympathetic function. There is some in vivo animal evidence that botulinum toxin can modulate the function of nociceptive neurons relevant to migraine (92). In humans, however, there is no definitive evidence that botulinum toxin results in any significant analgesia or anaesthesia, raising questions about the extent to which its effects are indeed mediated by uptake into nociceptive or sensory neurons. A property of clostridial toxins, including botulinum toxin, is that they undergo retrograde trans-synaptic transport into second-order neurons (93,94). This means that botulinum toxin may have effects in the brain, as well as in peripheral neurons.

Clinical trial evidence

There have been two large multicentre randomized clinical trials of the efficacy and safety of onabotulinum toxin A as a preventive therapy for chronic migraine (> 15 headache days per month) (95,96). The first study included 679 participants randomized (1:1) to receive injections of onabotulinum toxin A (155–195 U) or placebo every 12 weeks for two cycles (95). The primary end point was mean change from baseline in headache episode frequency at week 24. The study did not meet this end point, but it did meet secondary end points of reduction in headache days and migraine days. The

second study included 705 patients randomized (1:1) to receive injections of onabotulinum toxin A (155–195 U) or placebo every 12 weeks for two cycles (96). This study met its primary end point of mean reduction in frequency of headache days per 28 days from baseline to weeks 21–24 post-treatment, as well as multiple headache and quality-of-life-related secondary end points. The use of acute medications was not significantly reduced in either trial in patients treated with onabotulinum toxin A compared with those treated with placebo.

No serious adverse events were reported in the clinical trials for migraine.

Practical considerations

Medication overuse is common in patients with chronic migraine. Onabotulinum toxin A was found to be effective in reducing headache frequency in patients with medication overuse, but, on average, the onabotulim toxin A group did not have a reduction in acute medication use versus the placebo group. It is not clear whether reduction in the use of acute medication alone could have the same beneficial effect as preventive therapy with onabotulinum toxin A in patients with medication overuse, or if it could have an additive effect alongside with preventive therapy (97). Whether or not to withdraw patients from acute medications before initiating treatment with onabotulinum toxin A or any other preventive therapy remains a controversial issue (98).

Onabotulinum toxin A as a preventive therapy for migraine has the advantage that it needs to be administered only every 12 weeks, in contrast to most preventive therapies that are administered on a daily basis. The associated disadvantage is that it cannot be self-administered, requiring the time and expense of a physician visit.

Although few serious adverse effects have been reported in trials of onabotulinum toxin A for headache, multiple serious adverse effects have been reported with its use for other indications (99). Some adverse effects of onabotulinum toxin A may be under-reported, in part because of the lack of awareness that they may be associated with the treatment. One such adverse effect is headache (including exacerbation of headache in those with pre-existing headache). Severe headache has been reported as a complication of onabotulinum toxin A in patients receiving it for cosmetic indications (100). The exacerbation of headache as a consequence of onabotulinum toxin A may not be appreciated in patients who are already experiencing frequent headache. Flu-like symptoms have also been reported as a relatively common adverse effect of onabotulinum toxin A in patients receiving it for other indications (101). Here, again, it may be under-reported by physicians treating migraine patients because of the lack of awareness that this may be a related adverse effect rather than an unrelated event.

CGRP-targeted therapies

Treatments targeting CGRP are novel because of their specific development for migraine.

Monoclonal antibodies (mAbs) targeting CGRP or its receptor have now been studied as therapies for both episodic and chronic migraine in extensive phase II and III studies, involving approximately 10,000 patients to date. Three mAbs targeting CGRP are now approved for use in the United States, and are currently being evaluated for approved use worldwide.

Mechanism of action

CGRP release into the extracerebral circulation was observed following stimulation of the trigeminal ganglion, first in animal models then in humans (102), and in the superior sagittal sinus in animals (103). These findings led to investigation of migraine patients which showed that CGRP levels were elevated in the jugular blood during migraine attacks, and these elevated levels normalized following treatment of migraine with sumatriptan (104). Human triggering studies have provided evidence for a causative role for CGRP in migraine. Infusion of human αCGRP in patients with migraine without aura consistently evoked delayed headache (up to 6 hours after infusion), whereas infusion of placebo did not (105); in some patients the CGRP-evoked attack was consistent with migraine. Infusion of CGRP in patients with a diagnosis of migraine with aura also evoked headache, in some cases including aura (106). This substantial preclinical evidence led to the development of migraine therapies targeting CGRP, including both small molecules and mAbs. Four mAbs targeting CGRP have been developed for clinical use thus far. One of these, erenumab, binds to and inhibits the function of the CGRP receptor. The other three, eptinezumab, fremanezumab, and galcanezumab, bind the CGRP peptide and thereby inhibit its binding to cellular receptors.

Representative clinical trial data

Primary end points have been met in all of the clinical trials of the mAbs targeting CGRP thus far. No serious adverse events clearly related to any of the therapies have been identified, and overall they are reported to be very well tolerated, with minor skin site reactions representing the only common adverse event. In addition to the representative clinical trials described, multiple long-term safety and efficacy studies are ongoing.

Erenumab

A study investigating the use of erenumab as a treatment for episodic migraine randomized 317 patients to receive subcutaneous administration of 70 mg erenumab monthly for 3 months, 319 to receive 140 mg monthly, and 319 to receive placebo (107). The mean number of monthly migraine days was significantly reduced compared with placebo for both doses, and secondary end points of 50% responder rate, reduction in acute medication use, and improvement in impairment score were also met for both doses. Similar results were obtained in another randomized trial of erenumab for episodic migraine in which 577 patients were randomized to receive either erenumab 70 mg. subcutaneously or placebo monthly for 3 months (108). In a phase II study of patients with chronic migraine, 667 patients were randomized to receive either erenumab 70 mg, erenumab 140 mg, or placebo. Both doses met the primary end point of change in month migraine days from baseline in the last 4 weeks of double-blind treatment (weeks 9–12) (109).

Fremanezumab

A multicentre trial of fremanezumab for episodic migraine randomized 875 patients to receive either a single subcutaneous dose of 225 mg fremanezumab monthly, 675 mg quarterly, or placebo (110). Both dosing regimens showed a significantly greater reduction of monthly headache days at 12 weeks of treatment compared with placebo. In a study of patients with chronic migraine, 1130 were

randomized to receive either fremanezumab 225 mg monthly, 675 mg quarterly, or placebo (111). As with the study for episodic migraine, both dosing regimens met the primary endpoint of mean change from baseline in the average number of headache days per month during the 12-week study.

Galcanezumab

A 6-month trial examined the efficacy of two doses of galcanezumab, 120 mg and 140 mg delivered subcutaneously, for treatment of episodic migraine (112). In total, 858 patients were randomized to receive either dose of galcanezumab or placebo. Both doses met the primary end point of reduced monthly migraine days versus placebo, as well as all key secondary outcomes. A 3-month trial studied the efficacy and safety of galcanezumab, 120 mg with a 240-mg loading dose (n = 278), or 240 mg monthly (n = 277) versus placebo (n = 558) for the treatment of chronic migraine (113). Both dosing regimens met the primary end point of a significant mean reduction in monthly migraine headache days versus placebo.

Eptinezumab

A phase II study examined the efficacy, safety, and tolerability of eptinezumab 1000 mg versus placebo, delivered intravenously, for the treatment of patients with episodic migraine (114). The primary end points were safety at 12 weeks following infusion, and change from baseline in monthly migraine frequency in weeks 5–8 after the infusions. No safety concerns were identified, and there was a significant reduction in migraine days, which met the primary efficacy end point.

Practical considerations

The availability of these new therapies targeting CGRP raises important logistical questions regarding the preventive management of migraine. Where in the treatment algorithm for migraine should these new therapies be placed versus currently available therapies? Is there any predictor of response? Is there any advantage of one MAb over another? Is their benefit worth the cost?

As described in this chapter, currently available evidence-based migraine preventive therapies can be broadly categorized as antihypertensives, anticonvulsants, antidepressants, botulinum toxin (for chronic migraine), and neuromodulation devices (115). The choice of which therapy to initiate first, or second, or third, is not entirely straightforward. This decision is based on multiple factors, including predicted efficacy, tolerability, potential for serious adverse events, comorbid conditions, and cost. There are presently no 'biomarkers' or phenotypic indicators that predict response to specific therapies, and therefore the choice is often based on comorbidities (e.g. hypertension, insomnia, obesity) that may also be targeted by these treatments.

There have thus far been no head-to-head trials comparing efficacy, safety, and tolerability of previously available migraine preventive therapies with the mAbs targeting CGRP. The 'responder rate' analysis clearly indicates that for a subset of patients the mAbs targeting CGRP are dramatically effective in reducing migraine frequency—possibly more effective than any other class of migraine preventive treatments. Regarding cost, they are substantially more expensive than most of the current treatments.

With these considerations in mind, how should the mAbs targeting CGRP be prioritized relative to existing treatments? Their high cost and relatively limited 'real-world' experience with their efficacy and safety are factors that would favour their use only in individuals with a threshold frequency of migraine attacks who have failed other therapies. However, because they are the only migraine-specific preventive therapy that has been developed thus far, and they have the potential for substantially superior efficacy and better tolerability, it is not unreasonable to suggest that they should be considered as a 'first-line' therapy. These are very difficult questions that involve complex cost/benefit analyses. Further clinical experience is likely to better inform this analysis.

Neuromodulation therapies

Stimulation of branches of cervical and trigeminal nerves has been tried as an approach to acute and preventive therapy of migraine. Uncontrolled trials of implanted occipital nerve stimulators have shown promise as a treatment for chronic migraine, but no controlled study has reached a primary end point, and adverse events are common (116,117). Transcutaneous approaches have been developed as a less invasive and better-tolerated alternative to implanted stimulators.

Transcutaneous supra-orbital nerve stimulation

A double-blinded, randomized, sham-controlled trial examined the efficacy and safety of transcutaneous supraorbital stimulation as a preventive therapy for migraine (118). In total, 67 were randomized to receive either the treatment or sham stimulation with reduced pulse width, frequency, and intensity. Stimulation was administered daily for 20 minutes over a 3-month period. Transcutaneous supra-orbital stimulation was superior to sham for the two primary end points, namely reduction in mean number of migraine days and 50% responder rate. Treatment was also superior to sham for reduction in monthly migraine attacks, headache days, and acute medication use. No serious adverse events were reported.

In a follow-up observational study, 2573 patients who rented the transcutaneous supra-orbital stimulation device were surveyed (119). Of those, 2313 who used triptans as acute therapy were selected for study (as a way of selecting patients with migraine). Of these, 1077 (46.6%) were not satisfied and returned the device after a 40-day period, whereas 1236 (53.4%) were satisfied and purchased the device. Those who were not satisfied did not use the device for the recommended duration. Adverse events reported included discomfort with using the device, sleepiness, headache, and local skin irritation.

Practical considerations

The advantage of this device is that as a non-pharmaceutical approach it does not have the potential for systemic adverse effects, as is the case with medications. A disadvantage is that a significant percentage of patients find it uncomfortable to use. Also the recommended time of administration of 20 minutes per day requires a daily time commitment on the part of the patient

Transcranial magnetic stimulation

Single pulse transcranial magnetic stimulation (TMS) is approved in the United States and Europe for the acute treatment of migraine with aura, based on the results of a randomized, double-blind, sham-controlled study (120). More recent studies have suggested that single-pulse TMS may also have s benefit as a migraine preventive

therapy (121). In a non-blinded, non-controlled study, daily administration of single-pulse TMS was found to reduce headache days and associated symptoms in patients with both episodic and chronic migraine (121). A multicentre prospective open label observational study of 263 patients treated with four TMS pulses twice daily found reduction of headache days compared with a statistically derived placebo estimate (122). No serious adverse events were reported.

Practical considerations

As with supra-orbital nerve stimulation, single-pulse TMS has the advantage that it does not have the potential for systemic adverse events, as is the case for medications. It is therefore an appealing alternative for those for whom systemically administered therapies are contraindicated or poorly tolerated. As with other neuromodulation approaches, it does require a commitment of time to administer the treatment unlike self-administration of medications.

Conclusion

Substantial progress has been made in the prevention of migraine, and exciting new approaches have been introduced within the past few years. Despite this progress, however, there continues to be a large number of patients for whom currently available migraine preventive therapies are either ineffective or poorly tolerated. A better understanding of the pathophysiological mechanisms of migraine, including how these mechanisms may vary from patient to patient, is likely to lead to more specific, more effective, and better tolerated preventive treatments.

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16

Treatment and management

Non-pharmacological, including neuromodulation

Delphine Magis

Introduction

Migraine is a common disabling disorder and can significantly affect the patient's quality of life. However, according to a recent study, it appears that patients suffering from migraine seem reluctant to take preventive medications: 28.3% of episodic (International Classification of Headache Disorders, third edition (ICHD-3) beta criteria 1.1 or 1.2 (1)) and 44.8% of chronic migraineurs (ICHD-3 beta criteria 1.3 (1)) are current users of preventive drugs (2). Besides a lack of drug efficacy, another main reason for treatment discontinuation is the occurrence of side effects (range 34.8–49% in episodic migraineurs and 34.2–53.2% in chronic migraineurs, according to the drug class) (2). Thus, there is room for non-pharmacological migraine therapies with similar efficacies and fewer side effects than the main drugs usually prescribed for migraine prevention, i.e. beta blockers, antidepressants, antiepileptics, and calcium channel blockers. Of the available migraine preventive drugs, none was initially designed to treat that disease. Conversely, some non-pharmacological migraine treatments reviewed in this chapter opened the way to migraine-specific approaches.

Based on this author's experience, several types of patients are identified in whom non-pharmacological approaches can be proposed:

- patients who do not want to take any migraine preventive drugs for personal reasons, mainly the fear of harmful side effects;
- patients who have absolute or relative contraindications to the use of migraine preventive drugs;
- patients who are only partly improved by their migraine preventive medication, in order to avoid an additional preventive drug;
- patients who do not improve when on the main preventive drugs, or are considered as drug-refractory (3).

The topic of this chapter is broad and covers very different types of approaches. The more relevant therapies will be addressed and the placebo-controlled evidence, if available, will be concentrated on.

Oral therapies or 'nutraceuticals'

Oral non-pharmacological migraine preventive treatments can be separated into two main classes: the vitamins and other supplements, and the herbal remedies, for which the classification as 'non-pharmacological' is sometimes questionable, leading to the expression 'nutraceuticals'. The use of some metabolic enhancers involved in the Krebs cycle, like riboflavin, is particularly interesting because the rationale derives from previous migraine pathophysiological studies. Recently, this class of treatments was extensively reviewed (4,5).

Vitamins and other supplements

Riboflavin

The rationale for giving high doses of riboflavin (or vitamin B2) in migraine prophylaxis arose from brain spectroscopy studies performed in the early 1990s, which showed a reduction in mitochondrial phosphorylation potential in migraineurs between attacks (see also Chapter 15) (6). Riboflavin is a precursor of flavin mononucleotide and flavin adenine dinucleotide, which are coenzymes indirectly involved in electron transport in oxidation reduction reactions in the Krebs cycle (7). Therefore, riboflavin is an important co-factor of energy generation in the mitochondria, and was chosen for its potential therapeutic properties in increasing the mitochondrial phosphorylation that is supposed to be less effective in migraine patients. Hence, it had already been used in some inherited mitochondrial diseases and was able to improve the clinical and biochemical abnormalities in these patients.

Following an encouraging open pilot trial (8), Schoenen et al. performed a randomized controlled multicentre trial of high-dose riboflavin (400 mg) versus placebo in 55 patients suffering from episodic migraine (9). After 3 months of daily therapy, riboflavin was significantly superior to placebo in reducing attack frequency and headache days. The responder rate (i.e. patients with at least a 50% reduction in headache days) was 59% for riboflavin and 15%

for placebo ($P = 0.002$), and the number needed to treat (NNT) for efficacy was 2.3. Another double-blind crossover randomized controlled trial (RCT) was recently performed with riboflavin in 42 children, but only a dose of 50 mg was studied (10). After 16 weeks of therapy, no difference was found between real treatment and placebo groups, except for tension-type headache-like symptoms ($P = 0.04$) (10). The main shortcomings of this study were the young paediatric population (mean age 9 years), in whom the placebo effect is classically higher and the clinical evaluation more challenging, and the low doses of riboflavin used, which was based on a previous study (11). In that trial, the migraine preventive effect of a combination of 400 mg riboflavin, 300 mg magnesium, and 100 mg feverfew were compared to a placebo containing 25 mg riboflavin in 48 adult patients. There were no differences between the real treatment and 'placebo' groups, but both clinical outcomes were significantly positive (11). Recently, all available trials with riboflavin were reviewed, and it was concluded that riboflavin is a safe and well-tolerated option for preventing migraine symptoms in adults; however, there is insufficient evidence to make a firm recommendation regarding vitamin B2 as an adjunct therapy in adults and children with migraine (12).

The side effects of riboflavin are mild: gastrointestinal intolerance (1%), polyuria, and, exceptionally, a reversible cutaneous allergy (personal observation). The physician should inform patients that taking riboflavin, which is a water-soluble vitamin, usually changes the urine colour into a bright yellow/orange, which has no known consequences on health. An important point is that riboflavin does not induce any weight gain (or loss), contrary to most migraine preventive drugs.

The mechanism of action of riboflavin in migraine patients has become partly known from two studies (13,14). Sandor et al. (13) demonstrated that patients treated with daily riboflavin (400 mg) for 4 months did not show any evidence of brain excitability changes after treatment but it was effective, contrary to those treated with propranolol, suggesting radically different underlying pathophysiological mechanisms. In an elegant pharmacogenetic trial, Di Lorenzo et al. (14) treated 64 migraineurs with 400 mg riboflavin for 4 months, and blindly genotyped these patients for mitochondrial DNA (mtDNA) haplogroups. Forty patients responded to riboflavin ($P < 0.001$). The mtDNA analysis revealed that the outcome was better in patients with 'non-H' mtDNA haplotypes: 67.5% of them were responders, whereas 66.7% of 'H' were non-responders. The underlying mechanism is unknown but could be related to the association of 'H' haplotype with an increased activity in mitochondrial complex I, which is a major target for riboflavin. Thus, the treatment would be less effective in 'H' patients where complex I activity is optimal but could have a beneficial effect in haplotypes associated with a lower complex I activity (14).

Coenzyme Q10 and thioctic acid

Coenzyme Q10 and thioctic (α-lipoic acid) are other 'metabolic enhancers' that improve mitochondrial oxygen metabolism and adenosine triphosphate production, similarly to riboflavin (see also Chapter 15). Their efficacy was assessed in two randomized placebo-controlled trials (15,16). After the encouraging results obtained by Rozen et al. (17) in an open study, Sandor et al. (15) performed a randomized placebo-controlled trial with coenzyme Q10 q8h in 42 patients with episodic migraine. After 3 months of treatment, coenzyme Q10 significantly reduced attack frequency compared with placebo ($P < 0.01$), as well as the number of headache days ($P < 0.05$). The proportion of responders (who improved by at least 50% in frequency) was 47.6% for coenzyme Q10 versus 14.4% for placebo (NNT = 3). The tolerance profile was also excellent, with the exception of cutaneous allergy in one patient. Thioctic acid produces a clinical and biochemical improvement in various mitochondriopathies, and its preventive effect (600 mg/day) on episodic migraine was assessed in a double-blind placebo-controlled trial in 44 patients (16). The trial had to be interrupted because of slow recruitment and a time limitation on drug quality. The percentage of responders did not differ between thioctic acid and placebo. However, within-group analyses showed a significant reduction of attack frequency ($P < 0.01$), headache days ($P < 0.01$), and headache severity ($P < 0.05$) in patients treated with thioctic acid for 3 months, while these outcome measures remained unchanged in the placebo group. No adverse effects were reported. Larger and longer studies would thus be needed for this metabolic supplement.

Magnesium

The rationale for giving magnesium in migraine comes from magnetic resonance spectroscopy studies performed during and between migraine attacks (18,19), as well as the finding of low magnesium levels in various biological fluids interictally (20,21). Magnesium is mainly involved in energy metabolism and decreases neuronal excitability (22).

Three double-blind placebo-controlled trials have been done in migraine prophylaxis. The first study was performed in 20 women with menstrual migraine, receiving magnesium (360 mg/day) or placebo daily from ovulation to the first day of their next menstruations, over two cycles (23). Patients receiving magnesium had a significant reduction in headache frequency and total pain index. In the study by Peikert et al. (24), magnesium dicitrate (600 mg/dose) was used in 81 patients; the 50% responder rate for attack frequency was 52.8%, but the placebo-subtracted rate was only 18.4%. The last trial, using a drinkable aspartate salt of magnesium (20 mmol) was interrupted because of a lack of efficacy (25). In a recent review it was concluded that the evidence supporting oral magnesium is low (26). However, despite these mixed results, magnesium deserves to be prescribed for migraine prevention in some subsets of patients, for example children or females with menstrual-related migraines, at a recommended dose of 400 mg/day (27).

Intravenous magnesium was also experienced in acute migraine treatment. A recent meta-analysis of five RCTs using intravenous magnesium failed to demonstrate any beneficial effect in acute pain relief or need for rescue medication (28).

The usual side effects of magnesium are gastrointestinal (mainly diarrhoea).

Herbal medicines

Botanical or herbal treatment of headache was described in an Egyptian papyrus dated to 2500 BCE (see also Chapter 15). The number of plants believed to have some efficacy in migraine is huge, but evidence is sparse. As underlined in a recent review, there are several ways to prepare oral herbal medicines (dried, teas, infusions, capsules, etc.) and some important pitfalls, among them improperly prepared derivatives, loss of potency due to the method of preparation, ignorance of safety concerns, and unknown interactions with

drugs (29). Only butterbur and feverfew will be considered here as they have been employed in properly designed clinical studies.

Butterbur (*Petasites hybridus*) is a plant that flourishes in moist areas in Europe, and has been used for its analgesic and spasmolytic properties for centuries. Its mode of action is unknown, but it seems to have smooth muscle-relaxing effects and inhibits leukotriene synthesis. Its leaves are carcinogenic and hepatotoxic, so it is important to use preparations that only contain a special extract from the underground (rhizome) part of the plant. As far as its efficacy is concerned, Diener et al. (30) re-analyzed the outcome of a randomized placebo-controlled parallel-group study using 25 mg q8h of a special extract of butterbur root (Petadolex) for migraine prevention in 60 patients. The 50% responder rate for migraine frequency was 45% in the butterbur group and 15% in the placebo group after 3 months of therapy. Another larger RCT used butterbur extract 75 mg q12h, 50 mg q12h, or placebo q12h in 245 patients for migraine prevention (31). Over the 4 months of treatment, the 75-mg extract reduced migraine frequency by 48% ($P < 0.01$), the 50 mg extract by 36% (non-significant), and the placebo by 26%. The 50% responder rate for migraine frequency was 68% in the 75 mg-butterbur group versus 49% in the placebo group. The most frequent adverse events were mild gastrointestinal symptoms (mainly burping).

Feverfew (*Tanacetum parthenium*) has been known since the middle ages as a remedy against headache. The leaves of the plant (member of the daisy family) contain parthenolide, which inhibits nociception and neurogenic vasodilatation in the trigeminovascular system (32). In the study by Pfaffenrath et al. (33), three doses of a carbon dioxide extract of feverfew (MIG-99®; 2.08, 6.25, 18.75 mg q8h) were compared to placebo for migraine prevention for 12 weeks in 147 patients (33). Surprisingly, only the 6.25-mg dose was effective. The 50% responder rate for attack frequency was 27.8% in a sample of 36 patients, but the placebo effect turned out to be so high that the placebo-subtracted rate was negative (–3.6%). However, in a subset of 49 patients with at least four attacks/month the 50% responder rate was 36.8% versus 15.4% in the placebo group. In a further study led by the same authors (34), the migraine preventive effect of the 6.25-mg dose of feverfew q8h was compared to placebo in 170 patients during 16 weeks. The migraine frequency decreased significantly in the feverfew compared with the placebo group ($P < 0.05$). A Cochrane review concluded that the five eligible RCTs (1996–2003, among them the study by Pfaffenrath et al. (33)) provided insufficient evidence to suggest an effect of feverfew over placebo for preventing migraine (35).

More recently, a double-blind placebo-controlled trial assessed the efficacy of a sublingual association of feverfew and ginger for migraine acute treatment (36). Overall, 151 attacks were analysed in the active and 57 attacks in the placebo arm. At 2 hours, pain-free rates were 32% for feverfew/ginger versus 16% for placebo ($P < 0.05$), and pain relief occurred in 63% of subjects receiving active medication versus 39% for placebo ($P < 0.01$). This trial suggests that the association could help some patients treat their headache when the intensity is mild, but this needs to be confirmed by further studies

The most frequent adverse effects of feverfew are mouth ulcerations or inflammation, and loss of taste.

Exercise, behavioural therapies, and multidisciplinary care

Exercise

Exercise is recommended and has shown some efficacy in various neurological diseases; therefore, headache specialists commonly advise their patients to practise some regular aerobic exercise, but evidence of efficacy in migraine is lacking. Moreover, exercise per se is a well-known headache trigger (37). As underlined in a review by Busch and Gaul (34), most available studies are small pilot trials or case reports, and to date there have been no randomized placebo-controlled trials. The majority of studies did not find any significant reduction in headache frequency and only suggested an improvement of pain intensity in migraine patients due to regular exercise (5,38). One randomized trial compared the outcome in episodic migraineurs treated either with exercise (40 minutes, three times weekly), relaxation therapy, or topiramate (up to 200 mg/day) for 3 months (39). Final results were available for 72 patients. The number of migraine attacks significantly decreased in all groups when comparing the last month of treatment with the baseline period: –0.93 for exercise, –0.86 for relaxation, and –0.97 for topiramate. No significant differences were observed between groups. Migraine intensity only improved in the topiramate group. The authors concluded that exercise could be an alternative for patients who do not want to take or are intolerant to migraine preventive drugs (39).

Behavioural therapies

A meta-analysis of 55 studies reported the effectiveness of various biofeedback techniques (i.e. peripheral skin temperature biofeedback, blood volume pulse, and electromyography feedback) in migraine preventive management over 17 months of follow-up (40). In a recent RCT, Holroyd et al. (41) compared the effect of the addition of one of four preventive treatments to optimized acute treatment in 232 patients with episodic migraine (mean 5.5 migraines/month): beta blocker (n = 53), matched placebo (n = 55), behavioural migraine management plus placebo (n = 55), or behavioural migraine management plus beta blocker (n = 69) (41). The addition of combined beta blocker and behavioural migraine management (–3.3 migraines/month), but not the addition of beta blocker alone (–2.1 migraines/month) or behavioural migraine management alone (–2.2 migraines migraines/month), improved outcomes compared with optimized acute treatment alone (–2.1 migraines/30 days). The NNT was 3.1 for the addition of that combined therapy compared with optimized acute treatment alone, and 2.6 compared with beta blocker plus optimized acute treatment. Hence, the association of beta blockers and behavioural migraine management could improve the outcome of patients with frequent migraines (41). In chronic migraine with acute medication overuse (n = 84 patients), Grazzi et al. (42) also studied the consequence of adding (or not) a behavioural therapy management to pharmacological prophylaxis. Both groups improved significantly after 1 year, but the addition of behavioural therapy provided no superior benefit. However, these results are in contradiction with clinical data obtained previously by the same authors using a similar study design (43). After a 3-year follow-up, the population receiving biofeedback-assisted relaxation combined

with preventive drugs had a sustained improvement, contrary to patients taking drugs alone. The difference would be explained by a different relaxation programme between studies, i.e. a higher number of sessions in (43). Taken together, these results suggest that adding behavioural therapy to drug prophylaxis can be a useful and harmless method to achieve a better outcome in patients with frequent episodic or chronic migraine, although there is a lack of scientific proof (44).

The mode of action of behavioural techniques in migraine is obscure. They could help improve the global feeling of well-being, as MIDAS (Migraine Disability Assessment) scores appeared lower after biofeedback sessions (45). Moreover, biofeedback is related to muscle relaxation and decreased oxidative stress (45).

Integrated headache care and multidisciplinary treatment programmes

The management of patients suffering from chronic migraine with or without acute drug abuse is often challenging, as they often have several comorbidities (psychiatric, other chronic pain syndromes, etc.). The studies reported earlier (41–43) clearly demonstrate the need for a multidisciplinary approach to these patients, involving different disciplines, called integrated headache care (46). Structures including in- and outpatient care and treatment were therefore set up in various European countries (mainly Germany and Denmark) and in the United States (46). The outcome of patients treated by integrated headache care at the Essen Headache Centre (Germany) was recently published (47). The clinical data of 841 patients were prospectively collected over a 1-year follow-up period after the initial management. This management differed according to the 'phenotype' of the patient, ranging from psychologist or physical therapist counselling to a 5-day inpatient multidisciplinary treatment programme. The subsequent treatment had been provided by private neurologists. After 1 year, 36.4% had at least a 50% reduction in headache days, independent of their headache phenotype. An overall reduction of monthly headache days was seen in 57.8% of patients (mean reduction 5.8 ± 11.9 days) (47). Surprisingly, higher headache frequency at baseline and age > 40 years were associated with a better outcome. The 1-year follow-up data of the Headache Centre Berlin (Germany) are also available, but the study only included 201 patients with difficult-to-treat headaches, among them 11 with tension-type headache alone (48). A reduction of at least 50% in headache frequency was observed in 62.7% of patients, independent of their headache phenotype. A younger age (contrary to the Essen study) and fewer days lost at work/school were associated with a better outcome. Finally, in the Danish Headache Center's experience, 1326 headache patients had an overall significant reduction in headache frequency from 20 to 11 days/month ($P < 0.01$) and absence from work from 5 to 2 days/month ($P < 0.01$) (49). Predictors for good outcome were female sex, migraine, triptan overuse, and a frequency of 10 days/month, whereas tension-type headache and overuse of simple analgesics predicted a poorer outcome.

Acupuncture

Acupuncture belongs to the traditional Chinese medical armamentarium and is one of the most widely used non-pharmacological therapies in many diseases. In migraine, a recently updated Cochrane review analysed 22 randomised trials (4419 patients) where acupuncture was compared to routine care (no treatment), to 'sham' acupuncture (placebo), or to pharmacological prophylaxis (50). The first conclusion was that acupuncture provides additional benefit in the treatment of acute migraine attacks only or to routine care. However, there was no evidence of an effect of 'true' acupuncture over sham interventions. In an update of their Cochrane review, the authors came to a slightly different conclusion, i.e. that adding acupuncture to the symptomatic treatment of attacks reduces the frequency of headaches, but that, contrary to the previous findings, there is an effect over sham, but this effect is small (50). They added that available trials also suggest that acupuncture may be at least similarly effective as treatment with prophylactic drugs (50). Hence, in their large study on 794 episodic migraineurs, Diener et al. (51) demonstrated that the outcome after 26 weeks did not differ between patients treated with sham acupuncture, real treatment acupuncture, or standard drug preventive therapy (beta blockers, calcium channel blockers, or antiepileptics). The percentage of responders (decrease in migraine days by at least 50%) was 47% in the real treatment group, 39% in the sham acupuncture group, and 40% in the standard group ($P > 0.1$). In a former trial of migraine prevention, 302 patients had also been equally improved by real treatment and sham acupuncture (51% and 53% responders, respectively), but both were superior to a waiting-list group (15% responders) (52). More recently, another study reported only a clinically minor effect of various subtypes of acupuncture over sham procedures in migraine prophylaxis (53).

Thus, even if acupuncture can be considered as a valuable preventive therapy in migraine (50), this is also true for sham acupuncture given that the exact needle location seems to have no or limited importance. In a meta-analysis of relevant migraine studies, Meissner et al. (54) revealed that sham acupuncture was associated with higher responder ratios than oral pharmacological placebos (0.38 vs 0.22), which confirms that a relevant part of its overall effect may be due to non-specific—but nevertheless interesting—mechanisms.

Neuromodulation

Peripheral neuromodulation

Electrical stimulation of peripheral nerve(s) is a well-known way to treat pain within the nerve territory. In the first century AD the physician Scribonius Largus advised putting an electric fish on a painful area of skin in order to make the pain disappear. The analgesic effects of electrical stimulation have been attributed to several mechanisms: activation of afferent Aβ fibres, gate control in the spinal cord, and descending supraspinal control from the rostroventromedial medulla or the periaqueductal gray (55,56). Peripheral nerve stimulation (PNS) is widely used in chronic pain syndromes like neuropathic pain or the complex regional pain syndrome (57). Along the same line, PNS has been used to treat headaches, especially occipital neuralgia (58). In the last decade new emerging drugs for migraine prevention were quasi inexistent so headache clinical researchers turned to alternative, non-pharmacological therapies, among them PNS. The type of PNS was often chosen according to the migraine phenotype, as it can be invasive and applied continuously, or non-invasive and applied transcutaneously for short periods.

Invasive PNS

In migraine, like in other primary headaches, invasive PNS has been studied as a preventive therapy in the most disabled patients, i.e. patients chiefly suffering from drug-resistant chronic migraine. The most studied technique is great occipital nerve stimulation (ONS).

ONS

The initial rationale for using ONS came from findings of basic science studies showing the convergence of cervical, somatic, and dural (trigeminovascular) afferents on second-order nociceptors in the trigeminocervical complex (59,60). The effectiveness of great occipital nerve steroid injections in the prevention of various primary headaches also supported this rationale (61,62).

Besides small and/or heterogeneous open studies, three short-term (i.e. 3 months each) RCTs have been published (63–65). The preliminary findings of the Occipital Nerve Stimulation for the Treatment of Intractable Migraine (ONSTIM) study (n = 66 patients) suggested a reduction of at least 50% in headache frequency or a fall of 3 points on the intensity scale in 39% of patients treated with active ONS for 12 weeks, whereas no improvement was seen in sham or 'non-effectively' stimulated groups (64). In the sham-controlled Precision Implantable Stimulator for Migraine (PRISM) study (63), ONS did not produce any significant reduction in headache days in the 125 patients with drug-resistant migraine who completed the 12-week assessment period. However, this cohort was heterogeneous, as patients suffered either from migraine with or without aura, chronic migraine, and/or medication overuse headache. The latter could explain a less favourable outcome. Finally, Silberstein et al. (65) did another large study in 157 patients with chronic migraine, who were randomly assigned to active ONS or to sham stimulation, again for a 3-month period. No difference was found between the two groups as far as the percentage of responders (i.e. at least a 50% reduction in mean daily visual analogue scale (VAS) scores) was concerned. However, there was a significant difference in the percentage of patients that achieved a 30% reduction in VAS scores ($P < 0.05$). The decrease in the number of headache days was higher in the active group than in the control group ($P < 0.01$), as well as the decrease in migraine-related disability score ($P < 0.01$). The long-term results of this study were presented at the last International Headache Congress in Boston, June 2013 (66). After the 3-month randomized phase, the patients continued in an open-label phase of 40 weeks. Headache days were significantly reduced by 6.7 days for the intention-to-treat and 7.7 days for the intractable chronic migraine populations ($P < 0.01$), as well as disability scores. Patients' self-assessed relief and satisfaction were improved.

Besides the possible mechanisms of action described, ONS could act via non-specific modulatory effect on pain-control systems. Persistent hyperactivity in the dorsal rostral pons was reported with $H_2\,^{15}O$ positron emission tomography in chronic migraine patients treated with ONS (67).

Thus, these data highlight that ONS could offer a valuable alternative or add-on therapy for chronic migraine patients, but only after failure of several preventive medications and non-invasive, non-pharmacological treatments. Patients must be aware that improvement may be moderate or absent. Besides its invasiveness and cost, the technique may require several surgeries, which can result in complications like electrode migration or battery depletion (68).

In patients with medication overuse headache, it is crucial to perform effective detoxification before considering ONS, as drug overuse seems to be associated with a less favourable outcome (69).

Other types of invasive PNS

Internal left vagus nerve stimulation (VNS) has shown some effectiveness in refractory epilepsy. Only observational case reports or retrospective studies are available in migraine, mainly in patients treated for concomitant seizures. In a retrospective study by Lenaerts et al. (70), eight of 10 patients with migraine had at least a 50% reduction in headache frequency 6 months after VNS implantation versus the 3-month baseline period. The other surveys included a smaller number of patients, but reported overall a decrease of migraine frequency in about 50% of patients undergoing VNS (68).

The mode of action of VNS is obscure. It is believed to modulate several cortical and subcortical structures, among them areas involved in nociception.

A combination of ONS with supraorbital nerve stimulation (SNS) was performed by Reed et al. (71,72). In a retrospective study of 44 patients with chronic migraine (mean follow-up 13 months), the frequency of severe headaches decreased by 81% and half of the patients had nearly complete disappearance of headaches.

The sphenopalatine ganglion (SPG) is not a peripheral nerve per se but an extracranial autonomic structure lying in the pterygopalatine fossa, which has connections with the trigeminovascular system. The SPG had thus been previously targeted by various lesional procedures in order to alleviate pain in severe refractory primary headaches subtypes (68). Percutaneous high-frequency stimulation of the SPG has been performed in an open proof-of-concept study, and was able to relieve acute migraine attacks in five of 10 drug-resistant chronic migraine patients (73).

Non-invasive PNS

The neurostimulation techniques reviewed in the previous sections are invasive, and thus their use seems unsound in less disabled patients, like episodic migraineurs. The analgesic effects of transcutaneous electrical nerve stimulation (TENS) have been known for a long time, and the potential benefit of TENS on headaches have been suggested previously (74), but properly designed trials were lacking (75).

The effectiveness of a portable transcutaneous supraorbital nerve stimulator (tSNS) on episodic migraine prophylaxis has been recently evaluated in a randomized double-blind sham-controlled trial (76). Sixty-seven migraineurs (minimum of two attacks/month) were treated with daily tSNS or sham sessions of 20 minutes' duration. After 3 months, the mean number of migraine days decreased significantly in the tSNS group (6.94 vs 4.88; $P < 0.05$) but not in the sham group (6.54 vs 6.22 P = non-significant). The 50% responder rate was significantly greater in the tSNS group (38.1%) than in the sham group (12.1%; $P < 0.05$). Migraine attack frequency and acute drug intake were also significantly reduced in the real treatment but not in the sham group. The safety of tSNS and overall patient satisfaction were recently assessed in a study performed in the patients renting the tSNS device to treat their headaches (77). After an average testing period of 58.2 days, the majority (53.7%) of this population of 2313 patients were satisfied and kept the device. Among the unsatisfied patients, device analysis showed poor

compliance, as, on average, these patients used tSNS for less than 50% of the recommended time, and 4.5% of them did not even try the device on. Ninety-nine patients of the 2313 (4.3%) reported one or more adverse event(s), but none of them was serious. The mode of action of tSNS in migraine is currently unknown.

New devices thought to stimulate the vagus nerve transcutaneously (tVNS) have been developed. Preliminary open results have shown that these tVNS devices could help some patients (78). In recent overviews of neuromodulation trials in migraine, focusing on vagal nerve and sphenopalatine ganglion stimulation, it was concluded that these techniques offer promising options for the treatment of migraine (79,80).

Thus, non-invasive PNS, especially tSNS, may be proposed to a larger population of less disabled migraine patients as preventive or add-on migraine therapy, given that the rate of adverse events is very low and none is serious.

Challenges of PNS in migraine treatment

The use of PNS in migraine and headaches in general is associated with some issues in clinical studies and daily patient management. PNS per se provokes paraesthesia in the stimulated nerve territory, and therefore blinding is a real challenge in PNS sham-controlled trials, as they use the absence of stimulation or infra-threshold intensities as sham (68), sometimes after a first trial with effective PNS (65). It is thus imperative to enrol only PNS-naive patients for these studies. Moreover, like sham acupuncture, sham surgical treatments induce a higher response rate than oral drug treatments in migraine (proportion of responders 0.58 vs 0.22) (81). This could explain why the overall results of invasive PNS controlled studies are rather modest. These data are not available for non-invasive PNS. Finally, the compliance of patients treated with migraine preventive non-invasive PNS appears to be a real challenge. In the sham-controlled PREvention of MIgraine using Cefaly (PREMICE) tSNS study (76), patients applied the device 61% of the recommended time, whereas in the survey of the 2300 patients renting the tSNS device, the rate was 48.6% in patients finding the device 'ineffective', knowing that one out of five of the latter patients used the device for less than 60 minutes (77). This issue is unlikely in patients treated with invasive PNS. However, the recommended time of use is purely speculative (76).

Central non-invasive neuromodulation

Up to now only non-invasive central neurostimulation techniques have been used in migraine. Two main approaches are currently being studied: transcranial magnetic stimulation (TMS) and transcranial direct current stimulation (tDCS). Both are thought to be able to modulate the activity of the underlying brain area.

TMS

TMS has been employed in clinical neurophysiology since the late 1950s. It is able to modulate the excitability of the underlying cerebral cortex (depolarization or hyperpolarization), using a rapidly changing magnetic field delivered by a coil applied at the scalp surface. TMS allows the delivery of a single pulse (sTMS) or trains of repeated stimulations (rTMS). rTMS induces long-lasting changes in the underlying cortex; low stimulation frequencies (i.e. 1 Hz) have an inhibitory effect (82), whereas high frequencies (≥ 10 Hz) are excitatory (83). In healthy volunteers and migraine patients, rTMS was able to durably modify the excitability of the visual cortex, and, in consequence, to balance the electrophysiological abnormalities usually found in migraineurs (84,85), whereas sTMS disrupted cortical spreading depression in animal models (86). Thus, the application of TMS to migraine management was worthwhile.

Regarding the place of TMS in acute migraine attacks, a recent randomized sham-controlled trial was performed in 164 migraineurs with aura using a portable TMS device delivering two single pulses at 30-second intervals over the visual cortex, within the first hour of aura onset (87). Pain-free response rates at 2 h were 39% for TMS and 22% for the sham device ($P < 0.05$), and although significant the overall therapeutic gain was of 17% only. Sustained pain-free rates at 24 h and 48 h were in favour of TMS, but headache response at 2 h, use of acute medication, or consistency of response did not differ between groups. The eligible population of this study had between two and eight migraine with aura episodes per month; it was not clearly stated if some patients met the criteria for chronic migraine (ICHD-3) (1). Hence, the efficacy of TMS in the treatment of acute migraine attack needs to be confirmed by further studies.

The efficacy of rTMS in migraine prevention has only been investigated in a few small studies. Based on the hypothesis that the left dorsolateral prefrontal cortex (LDLPFC) would exert a pain-reducing top-down control and is hypoactive in chronic migraine, Brighina et al. (88) applied high-frequency rTMS (20 Hz) or sham stimulation to the LDLPFC in 11 chronic migraineurs. After 12 sessions of rTMS, the attack frequency, headache index, and use of acute medications were reduced, and this effect lasted up to 2 months. There was no significant improvement in the five patients receiving the sham stimulation. These positive results were not confirmed by another study where 13 patients with chronic migraine also received high-frequency rTMS (10 Hz) over the LDLPFC, which turned out to be less effective than placebo (89). In episodic migraine the cortical pre-activation level and the habituation of sensory cortices to repeated stimulations seem reduced (90). This is not the case in chronic migraine, where the electrophysiological studies suggest heightened cortical pre-activation levels, like in a 'never-ending attack' (90,91). It is likely that the therapeutic effect of rTMS is not linear and will depend on the baseline activation level of the underlying cortex and thus the stimulation parameters will have to vary according to the migraine subtype (68). Based on this assumption, inhibitory quadripulse (QP) rTMS (92) was applied over the visual cortex in 16 chronic migraine patients during a 4-week pilot trial (two rTMS sessions a week as add-on therapy) (93). A majority of patients improved significantly after QP rTMS therapy. Monthly migraine days decreased, on average, from 22 before to 13 after QP rTMS (–41%; $P < 0.05$) and severe attacks were reduced by 25% ($P < 0.05$). The 50% responder rate was 38%, while half of patients reversed from the chronic to the episodic form of migraine. Acute medication intake was significantly decreased (–55.5%; $P < 0.05$). The clinical improvement remained stable at least 1 month after the end of QP rTMS, with an average of 10.9 migraine days per month (–50.5% vs baseline; $P < 0.05$) (93). There were no adverse events and, interestingly, medication overuse did not modify the response to QP rTMS therapy.

tDCS

tDCS has been known and applied to treat neurological disorders since the nineteenth century. Nowadays it is a safe central

neuromodulation technique. tDCS uses weak currents to modify the cell's resting membrane potential, leading to focal modulation of cortical excitability. As in rTMS, opposite effects can be obtained with tDCS: cathodal stimulation inhibits neuronal firing, whereas anodal stimulation increases it. In healthy volunteers, tDCS is able to modulate resting electroencaphalography and event-related potentials (94), and functional connectivity of corticostriatal and thalamocortical circuits (95). This is of particular interest for migraine as it is thought to be associated with thalamocortical dysrhythmia (96).

The effect of tDCS on migraine attack was evaluated in a sham-controlled trial involving 62 patients suffering from chronic migraine (97). Surprisingly, both tDCS (so far, this trial is only available in abstract form and thus the polarity is unknown) and sham stimulation led to a 54.2% reduction in headache intensity, suggesting a non-specific placebo effect.

DaSilva et al. (98) performed another sham-controlled trial in 13 patients, using anodal tDCS applied over the primary motor cortex for chronic migraine prevention. They noticed a delayed effect on pain intensity and duration (120 days after stimulation), which was attributed to slow modulation of central pain-related structures (98).

In a proof-of-concept study, Vigano et al. (99) evaluated the preventive effect of an 8-week anodal tDCS therapy over the visual cortex in 10 episodic migraineurs (two sessions/week). Migraine attack frequency, migraine days, attack duration, and acute medication intake significantly decreased during the treatment period compared with pretreatment baseline ($P < 0.05$), and this benefit persisted, on average, 4.8 weeks after the end of tDCS. Moreover, an electrophysiological assessment found that a single session of anodal tDCS over the visual cortex was able to increase habituation to repetitive visual stimuli in healthy volunteers and in episodic migraineurs (99), who, on average, lack habituation interictally (90). That anodal tDCS has a significant preventive anti-migraine effect suggests that the low pre-activation level of the visual cortex in migraine patients can be corrected by an activating neurostimulation (99). A larger sham-controlled trial would thus be worthwhile.

Conclusion

The diversity of non-pharmacological migraine treatments is gradually increasing and offers new therapeutic possibilities and hope for patients. Occipital single-pulse TMS and transcutaneous SNS have the strongest evidence (100). tDCS and repetitive magnetic stimulation have been promising in pilot studies, but large sham-controlled trials are not yet available (100). For supraorbital transcutaneous stimulation, TMS, and external VNS, there exists one or two double-blind, sham-controlled RCTs, all with favourable outcomes and no severe or dangerous adverse events (101).

The majority of the treatments reviewed here are harmless and their efficacy often seems within the range of usual migraine preventive drugs.

In the most disabled patients it would be worthwhile setting up multidisciplinary approaches, including alternative therapies (among them non-invasive neurostimulation), before turning to more invasive and expensive devices in chronic treatment-resistant patients (102).

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PART 3

Trigeminal autonomic cephalgias

17. **Classification, diagnostic criteria, and epidemiology** *177*
Thijs H. Dirkx and Peter J. Koehler

18. **Cluster headache: clinical features and management** *182*
Ilse F. de Coo, Leopoldine A. Wilbrink, and Joost Haan

19. **Paroxysmal hemicrania: clinical features and management** *190*
Gennaro Bussone and Elisabetta Cittadini

20. **SUNCT/SUNA: clinical features and management** *196*
Juan A. Pareja, Leopoldine A. Wilbrink, and María-Luz Cuadrado

21. **Hemicrania continua** *203*
Johan Lim and Joost Haan

22. **Cluster tic syndrome and other combinations of primary headaches with trigeminal neuralgia** *208*
Leopoldine A. Wilbrink, Joost Haan, and Juan A. Pareja

17

Classification, diagnostic criteria, and epidemiology

Thijs H. Dirkx and Peter J. Koehler

Introduction

The trigeminal autonomic cephalalgias (TACs), including cluster headache, paroxysmal hemicrania, SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing), SUNA (with cranial autonomic symptoms) and hemicrania continua, belong to the primary headaches. They are characterized by severe unilateral headache in association with ipsilateral cranial autonomic features, such as lacrimation, conjunctival injection, and nasal symptoms. The TAC concept was first proposed by Goadsby and Lipton in 1997 (1). They classified short-lasting primary headache syndromes into those exhibiting marked autonomic activation (TACs) and those without autonomic activation. They hypothesized a pathway of activation between trigeminal afferents (giving rise to pain) and cranial parasympathetic efferents (giving rise to cranial autonomic features), hence the name trigeminal autonomic cephalalgias. Cranial sympathetic dysfunction may also be observed, but this is considered a secondary phenomenon. These headaches are frequently associated with features typically associated with migraine, including nausea, photophobia, and phonophobia, whereas migraine aura is rarely observed. The differences between the various clinical syndromes within the TAC group are mainly based upon differences in attack frequency and duration; they share the typical severe pain and autonomic symptoms. Cluster headache is the best known and most frequent headache type within the group of trigeminal autonomic cephalalgias (see Chapter 18). Cluster headache, sometimes also described as 'suicide headache', is known as the most painful of head pains and one of the most severe pain disorders known to man. The other TACs have a much lower prevalence, although the epidemiological literature on this issue is limited.

In this chapter we will briefly discuss the concept of TACs, the different clinical syndromes, diagnostic criteria, and epidemiology. In the following chapters each of the TACs will be discussed separately and in more detail.

Classification

According to the most recent International Classification of Headache Disorders (ICHD-3) criteria, four types of headache may be distinguished among the TACs, with several subdivisions (**Box 17.1**) (2). The first ICHD criteria (1988) described cluster headache (episodic and chronic) and chronic paroxysmal hemicrania (3). The concept of TACs was adopted in the ICHD-2 criteria (4) and, furthermore, the diagnoses of episodic paroxysmal hemicrania and SUNCT were added in this edition (2005).

Hemicrania continua (see Chapter 21) was not described as one of the TACs in the ICHD-2 criteria owing to its more or less continuous character and as cranial autonomic features were believed to be 'less constant' (4, p.61). At the time, it was classified among 'Other primary headaches' (4.7). It was included in ICHD-3 as one of the TACs based on the fact that the pain is typically unilateral and during superimposed exacerbations of severe, intense pain, there are typical autonomic symptoms (similar to the other TACs). Brain imaging studies showed activation of the posterior hypothalamic area in hemicrania continua, which is also seen in cluster headache and other TACs. Moreover, the absolute response to indomethacin is comparable to that in paroxysmal hemicrania (5). However, brain imaging studies also showed activation of the dorsal pons in hemicrania continua, which is more similar to the imaging findings seen in episodic and chronic migraine (5).

In ICHD-3, short-lasting unilateral neuralgiform headache attacks (SUNHA) are subdivided into SUNA and SUNCT. '*Probable* trigeminal autonomic cephalalgia' is mentioned as a separate category in the ICHD-3. These are headache attacks that are believed to be a type of TAC, but which are missing one of the features required to fulfil all the criteria.

Both chronic and episodic forms of cluster headache (see Chapter 18), paroxysmal hemicrania (see Chapter 19), and SUNCT/SUNA (see Chapter 20) are described. In cluster headache, the episodic form is more frequent than the chronic form. Paroxysmal hemicrania and SUNCT/SUNA usually have a chronic course (6).

Box 17.1 ICHD-3 criteria for trigeminal autonomic cephalalgias (TACs)

- **3** Trigeminal autonomic cephalalgias (TACs)
  - **3.1** Cluster headache
    - 3.1.1 Episodic cluster headache
    - 3.1.2 Chronic cluster headache
  - **3.2** Paroxysmal hemicrania
    - 3.2.1 Episodic paroxysmal hemicrania
    - 3.2.2 Chronic paroxysmal hemicrania
  - **3.3** Short-lasting unilateral neuralgiform headache attacks
    - 3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)
      - 3.3.1.1 Episodic SUNCT
      - 3.3.1.2 Chronic SUNCT
    - 3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA)
      - 3.3.2.1 Episodic SUNA
      - 3.3.2.2 Chronic SUNA
  - **3.4** Hemicrania continua
    - 3.4.1 Hemicrania continua, remitting subtype
    - 3.4.2 Hemicrania continua, unremitting subtype
  - **3.5** Probable trigeminal autonomic cephalalgia
    - 3.5.1 Probable cluster headache
    - 3.5.2 Probable paroxysmal hemicrania
    - 3.5.3 Probable short-lasting unilateral neuralgiform headche attacks
    - 3.5.4 Probable hemicrania continua

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Remitting and unremitting types of hemicrania continua are also distinguished (2).

Primary or secondary

TACs belong to the primary headaches. However, the typical headache syndromes, fulfilling ICHD-3 criteria, have also been described in association with other disorders (e.g. intracranial mass lesions and vascular lesions). If a TAC occurs for the first time in close relation to another disorder that is known to cause headache, it should be diagnosed as a secondary headache (2). In comparison with migraine there is a higher incidence of underlying lesions in TACs, although the exact frequency is unknown. If the prevalence of cluster headache is estimated at 0.1% (7), it is of interest to see that in a series of 84 pituitary tumours, TACs were found in 10% of patients, i.e. 100 times more prevalent (8). Although still rare, cluster headache, in particular, is well known to be secondary to intracranial disorders. A 2010 review identified 156 cases presenting with 'cluster-like headache' (9). The most frequent pathologies were of vascular origin, for example aneurysms, arteriovenous malformations, and carotid artery dissection (38.5%, n = 57). Tumours represented 25.7% (n = 38) of the cases, of which five were pituitary tumours. Another review (2014) reported 10 pituitary tumours out of 25 patients developing cluster headache secondary to a tumour (10). Of the patients in the 2010 review (9), for whom sufficient data were available, 50% matched the ICHD-2 criteria for cluster headache. Because of these perfect mimics, the authors advised magnetic resonance imaging (MRI) in all patients presenting with cluster headache.

As they are less prevalent, not much is known about other TACs with respect to secondary headache; however, multiple secondary cases have been described for all TACs. Symptomatic SUNCT, caused by vascular conflict of the trigeminal nerve with an artery, has been described in numerous case reports (11). To exclude underlying causes, imaging (MRI) is advised in all newly diagnosed TACs.

Epidemiology

Cluster headache is the most frequent type of headache among the TACs and a considerable number of epidemiological studies have been conducted. A meta-analysis of population-based studies in 2008 estimated its lifetime prevalence at 124 per 100,000 persons (95% confidence interval 101–151), or approximately 1:1000 persons. The 1-year prevalence was 53 per 100,000 (7). The male-to-female ratio is 4.3. Episodic cluster headache is much more frequent than chronic cluster headache, with a ratio of 6.0 (7). Cluster headache can develop at any age; peak age of onset is between 20 and 29 years. In women with episodic cluster headache a second peak of onset occurs in the sixth decade. In women with chronic cluster headache, the average age of onset is significantly higher, with a mean age of 51 years (12). The exact prevalence of the other TACs is unknown. In a large review on the epidemiology of headache it was stated that insufficient data were available to make a reliable statement on the prevalence and incidence of the TACs except for cluster headache (13). The following studies give an estimate on the prevalence of the other TACs.

The reported incidence of paroxysmal hemicrania is around 1–3% of cluster headache (14) or one in 50,000 (15). One study showed that 20% suffered from episodic paroxysmal hemicrania and 80% had a chronic course (16). In their review on TACs (6), Goadsby et al. estimated a chronic course in 65% of patients. As episodic paroxysmal hemicrania was mentioned for the first time in the ICHD-2 criteria, older studies focus mainly on chronic paroxysmal hemicrania alone. A 2008 study did not confirm a female predominance in 31 patients (16). Previous studies, however, show a higher prevalence in women. In a study of 74 patients, 62% were female (17). In the same study the mean age of headache onset was 41 years (range 6–75 years).

SUNCT and SUNA have been considered rare conditions. An Australian study estimated the prevalence of SUNCT/SUNA at 6.6 per 100,000. An episodic disease course was evident in 58% of 24 patients; the remaining had a chronic course (18). In another study of 52 patients, 43 had SUNCT and nine SUNA. In contrast to the previous study they found that only 13% of patients with SUNCT and no patients with SUNA had the primary episodic form of the disease (19). In a literature review of 222 cases the mean age at onset was 47.6 years. The SUNCT group consisted of 109 men and 74 women versus 11 men and 19 women with SUNA (20).

Hemicrania continua seems more frequent than SUNCT/SUNA and paroxysmal hemicrania. Some claim it is underdiagnosed, but the exact prevalence is unknown. It may be frequently misdiagnosed as chronic tension type headache or chronic migraine. In one study 24 out of 34 patients were women and the mean age of onset was 28 years (range 5–67 years) (21).

At the level of reference centres, the following figures are available. In a general neurology clinic in the UK, headache was the primary complaint in 23.4% of 3394 patients (22). Forty patients were

diagnosed with a TAC (1.2% of all referrals, 5.3% of all headache patients), of which 36 had cluster headache and four SUNCT/SUNA. None of the patients was diagnosed with paroxysmal hemicrania. Three patients were diagnosed as having hemicrania continua, which was not classified as a TAC at the time.

In a large retrospective study in a tertiary headache centre in China, 1843 patients (1152 women) were diagnosed according to the ICHD-2 criteria. Ninety-eight patients (5.3%) were diagnosed as having trigeminal autonomic cephalalgia, and cluster headache was the most common subtype (n = 83). The remaining 15 cases included 10 patients with probable cluster headache and five with SUNCT. Patients with paroxysmal hemicrania were not found in this study. Hemicrania continua was not specifically mentioned in this study, but was classified under other primary headaches, with a combined prevalence of 1.5% (23).

In a tertiary headache clinic in Spain, 1000 patients were diagnosed according to the ICHD-2 criteria. Twenty-six (2.6%) were diagnosed as having trigeminal autonomic headaches, including 20 patients with cluster headache, four with paroxysmal hemicrania, and two with SUNCT. Moreover, 16 patients were diagnosed with hemicrania continua, which is a relatively high incidence compared with other studies (24).

Looking at population-based epidemiological studies the following data are of interest. In the Vågå study on headache epidemiology, all residents of the Norwegian town of Vågå aged 18–65 years old, were asked to participate; 1838 persons (88.6%) were included. They were screened for many types of headache by way of a headache questionnaire. Seven patients with cluster headache were found, resulting in a prevalence of 0.3 (25). Two patients with possible SUNCT/SUNA and one possible case of chronic paroxysmal hemicrania was found. Eighteen patients reported a headache syndrome that was suggestive of hemicrania continua. These diagnoses were labelled probable, because an indomethacin test (which is necessary for a definite diagnosis) could not be conducted (26).

To summarize, cluster headache is the most frequent of the TACs. Epidemiological data on the other TACs are scarce and variable. The studies discussed above suggest that hemicrania continua is probably the second most prevalent TAC. SUNCT/SUNA and paroxysmal hemicrania are very rare.

Distinguishing between the TACs

The various types of TAC are not only distinguished by differences in attack frequency and duration, but also by differences with respect to the response to treatment (6). Cluster headache has the longest attack duration (15–180 minutes). By definition, the attack frequency is typically between one attack in 2 days to a maximum of eight attacks a day. Typical for cluster headache is the nocturnal occurrence of attacks and, of course, the cluster periods. Paroxysmal hemicrania has an intermediate attack duration (2–30 minutes) and a median frequency of 11 attacks daily (16). SUNCT/SUNA has the shortest attacks (1–10 minutes) and the highest attack frequency (up to 100 attacks daily). Several different attack patterns of SUNCT/SUNA are described (see Chapter 20). Hemicrania continua has a more continuous dull pain with exacerbations that may include the typical autonomic symptoms and severe pain. The autonomic symptoms tend to be less prominent than the in other TACs.

The characteristics of these headaches will be further discussed in the next chapters. A conveniently arranged overview with respect to the distinctions between the TACs is presented in Table 17.1.

Differential diagnosis

The TACs can usually be recognized easily by an adequate description of attack characteristics, frequency, and duration. No laboratory or radiological tests are available to confirm the diagnosis.

It is of importance to realize that cranial autonomic symptoms, as seen in the TACs, may be observed in other types of headache as well, but usually they are more severe in TACs. A typical feature of TAC is the lateralization of autonomic symptoms ipsilateral to the side of the headache. Likewise, migrainous symptoms (photophobia and phonophobia), are also more frequently ipsilateral to the headache in TACs, compared to migraine, where these symptoms are

Table 17.1 Characteristics of cluster headache, paroxysmal hemicrania, and SUNCT/SUNA

	Cluster Headache	Paroxysmal Hemicrania	SUNCT/ SUNA
Sex	3M to 1F	M = F	1.5M to 1F
Pain			
Quality	Sharp/stabbing/ throbbing	Sharp/stabbing/ throbbing	Sharp/ stabbing/ throbbing
Severity	Very severe	Very severe	Severe
Distribution	V1> C2> V2> V3	V1 > C2> V2> V3	V1> C2> V2> V3
Attacks			
Frequency (typical day)	1-8	11	100
Length (typical in minutes)	30-180	2-30	1-10
Triggers			
Alcohol	+++	+	–
Nitroglycerin	+++	+	–
Cutaneous	–	–	+++
Agitation/restlessness	90%	80%	65%
Episodic vs chronic	90:10	35:65	10:90
Circadian/circannual periodicity	Present	Absent	Absent
Treatment effects			
Oxygen	70%	No effect	No effect
Sumatriptan 6 mg	90%	20%	< 10%
Indomethacin	No effect	100%	No effect
Migraine features with attacks			
Nausea	50%	40%	25%
Photophobia/ phonophobia	65%	65%	25%

* Based on several cohorts and patients seen in practice.[16,19,33]

SUNCT/SUNA, short-lasting unilateral neuralgiforrn headache attacks with conjunctival injection and tearing/short-lasting unilateral neuralgiform headache attacks with cranial autonomic features; M, male; F, female; C, cervical; V, trigeminal

Reproduced from *Seminars in Neurology*, 30, Goadsby PJ, Cittadini E and Cohen AS, Trigeminal Autonomic Cephalalgias: Paroxysmal Hemicrania, SUNCT/SUNA,and Hemicrania Continua, pp. 186–91. © 2010 Georg Thieme Verlag KG.

most often bilateral (6). An important feature of cluster headache (and also other TACs) is a sense of restlessness during attacks. This is a characteristic difference to individuals with migraine, who tend to remain as still and as quiet as possible.

In some cases it may be difficult to distinguish between the different TACs. The clinical syndromes of paroxysmal hemicrania and SUNCT/SUNA may sometimes be very similar. Differentiating between these is important considering the treatment consequences. As paroxysmal hemicrania has an absolute response to indomethacin, a trial of indomethacin treatment is recommended when there is clinical uncertainty about the diagnosis.

Hemicrania continua may be confused with other forms of unilateral chronic daily headache (e.g. migraine or chronic tension type headache), but also with cluster headache, in which a dull background headache may persist between attacks. If there is one-sided headache and doubt about the diagnosis, again, a trial treatment with indomethacin may be considered (21).

SUNCT/SUNA may be confused with trigeminal neuralgia (TN) (27). In some patients both the ICHD criteria for TN as for SUNCT/SUNA are fulfilled. Autonomic symptoms have been described in TN; however, they are considered to be more prominent in SUNCT/SUNA. Autonomic symptoms in TN tend to develop after several years. Furthermore, TN attacks tend to be shorter. The mean duration of a SUNCT attack is 61 seconds (5–250 seconds) (28), while for TN the duration is 1–60 seconds, with most attacks lasting only several seconds (29). In both TN and SUNCT, patients are sensitive to cutaneous triggers. In TN there is typically a refractory period following a trigger; this is not found in SUNCT/SUNA. In TN, < 5% of cases involve the first trigeminal division (V1) only, whereas in SUNCT, attacks confined to V1 are typical. Rare cases of patients presenting with cluster headache (or even less frequently paroxysmal hemicrania) and TN simultaneously have been described (the cluster tic syndrome; see Chapter 22).

Pathophysiology

The pathophysiology of TACs is still not completely understood. The name indicates the hypothesis that activation of the trigemino-autonomic reflex may be part of the pathophysiological mechanism (Figure 17.1). Pain afferents from the trigeminal nerve project to the thalamus and cortical areas leading to the awareness of pain. Activation of the trigeminal nerve also causes reflex activation of the parasympathetic outflow from the superior salivatory nucleus via the facial nerve. This results in the typical autonomic symptoms, including lacrimation, reddening of the conjunctiva, and nasal congestion. It also acts as a positive feedback system resulting in dilatation of blood vessels, thereby leading to a further stimulus of trigeminal afferent nociceptors (30). This may be the final common pathway by which the typical symptoms of the TACs develop.

There is evidence that the hypothalamus plays a central role in the pathophysiology of the TACs. Positron emission tomography and MRI studies show hypothalamic hyperactivity ipsilateral to the side of the headache in cluster headache, contralateral in paroxysmal hemicrania, and bilateral in SUNCT during attacks (31). A key role of the hypothalamus may explain the typical rhythm of attacks in TACs.

A dysfunction in the hypothalamus, or other areas of the pain matrix, may lead to a permissive state, in which the trigeminal autonomic reflex is dysregulated, which may cause the typical pain and autonomic symptoms. The posterior hypothalamus may play a part in terminating attacks, thereby regulating the duration of individual attacks and therefore be responsible for the different TAC types (32). It is striking, however, to realize that the optimal treatment regimens for the different TACs are not the same, which implies a different pathogenesis. For example, the excellent response to indomethacin in paroxysmal hemicrania and hemicrania continua is not found in cluster headache or SUNCT/SUNA. Cluster headache attacks respond to oxygen and triptans; furthermore, attack frequency is greatly reduced by verapamil. SUNCT/SUNA has been difficult to treat. Successful results have been described with lamotrigine, gabapentin, and topiramate.

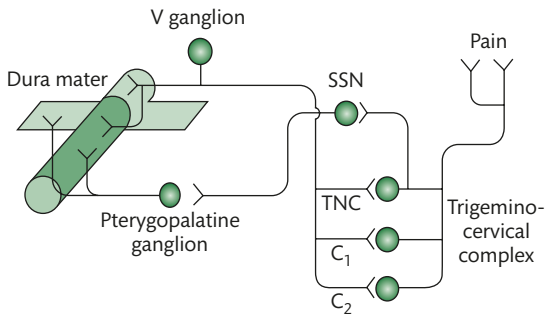

Figure 17.1 Trigemino-autonomic reflex.

SSN, superior salivatory nucleus; TNC, trigeminal nucleus caudalis.

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Conclusion

Cluster headache is the most frequent headache type of the TACs. The other TACs are rare, but epidemiological data are scarce and variable. The TACs are characterized by typical unilateral headache attacks with associated ipsilateral cranial autonomic symptoms. The various types of TAC are not only distinguished by differences in attack frequency and duration, but also by differences with respect to the response to treatment. There is some evidence for a shared pathophysiology in all TACs.

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18

Cluster headache

Clinical features and management

Ilse F. de Coo, Leopoldine A. Wilbrink, and Joost Haan

Introduction

Cluster headache is a well-defined primary headache syndrome, characterized by unilateral short attacks of excruciating pain located in the orbital, supraorbital, or temporal region. In the typical form, the attacks are accompanied by ipsilateral cranial autonomic features of the eye and nose (1,2).

The first description was probably made by the famous Dutch physician, anatomist, and mayor of Amsterdam, Nicolaes Tulp (1593–1674) in the seventeenth century (3). Over the years the headache was given many names, such as Horton's disease, migrainous neuralgia, and hemicrania neuralgiformis chronica. The name cluster headache was established in 1952 and refers to the typical episodic character of the syndrome such as it occurs in the majority of patients (4,5).

Epidemiology

The prevalence of cluster headache is about 1 in 1000 persons (6), making it much rarer than migraine. The male to female ratio is 4.3:1. Peak age of onset is between 20 and 29 years (6–8), but cluster headache can start at any age. There are many reports of young children with cluster headache; descriptions of cluster headache in octogenarians or older are, however, very exceptional. More about the epidemiology of cluster headache can be found in Chapter 17.

Clinical features, physical examination, and imaging

Patients with cluster headache suffer from attacks of severe-to-very severe unilateral pain, which is located in the orbital, supraorbital, and/or temporal regions (2). Rarely, patients experience bilateral pain during an attack. Side shifting between headache attacks or cycles, however, is reported by 14–38% of patients (9,10).

According to the current criteria (**Box 18.1**), cluster headache attacks last between 15 and 180 minutes, but a longer duration of attacks has been reported, especially in females (11). Attacks occur from once every other day to a maximum of eight per day. A bout or episode is a period in which frequent cluster headache attacks occur. Such a period may last from weeks to months. Patients with cluster headache are often restless during an attack, and most have ipsilateral autonomic symptoms such as lacrimation (91%), conjunctival injection (77%), nasal congestion (75%), ptosis, eyelid oedema, rhinorrhoea, forehead and facial sweating, miosis, aural fullness, and/or facial flushing. These symptoms disappear after the attack, although ptosis and/or miosis can also persist outside attacks. In a minority of patients, cluster headache attacks can also be accompanied by nausea and vomiting. Patients can experience an aura preceding their attacks, which can exist of fully reversible visual symptoms, sensory symptoms, speech disturbances, or a combination of these. Motor, brainstem, or retinal symptoms are very rare (12–14). Pre- and postictal symptoms are very frequent (15). During attacks, allodynia can occur (16).

Cluster headache can be divided into an episodic and a chronic form. Most patients (approximately 80%) have the episodic form, which is defined as a lifetime occurrence of at least two cluster periods lasting more than 7 days to 1 year, separated by pain-free remissions periods of more than 3 months. The remaining 20% are diagnosed with the chronic form, which is defined as having attacks for more than 1 year without remissions that last longer than 30 days. In the episodic form the mean duration of a bout is around 8.6 weeks (9). Many patients have one bout per year, but patients can also stay attack-free for many years. A change from the episodic to the chronic form (secondary chronic cluster headache) and vice versa (secondary episodic cluster headache) can occur (17–20). In a 10-year follow-up study of 189 patients, about 13% of episodic cluster headache patients became chronic and about 30% of chronic cluster headache patients became episodic (17).

There are several triggers for individual attacks when patients are in an active episode, such as alcohol, vasodilators, daytime naps, changes in air pressure (airplane, diving), weather changes, and certain odours (1,10,20–23). Remarkably, these triggers do not cause headache outside an active episode/bout.

Box 18.1 ICHD-3 criteria for diagnosing cluster headache

A At least five attacks fulfilling criteria B–D.
B Severe or very severe unilateral orbital, supraorbital, and/or temporal pain lasting 15–180 minutes (when untreated)
C Either or both of the following:
  1 At least one of the following symptoms or signs, ipsilateral to the headache:
    a. Conjunctival injection and/or lacrimation
    b. Nasal congestion and/or rhinorrhoea
    c. Eyelid oedema
    d. Forehead and facial sweating
    e. Miosis and/or ptosis.
  2 A sense of restlessness or agitation.
D Occurring with a frequency between one every other day and eight per day.
E Not better accounted for by another ICHD-3 diagnosis.

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Studies of large cluster headache cohorts have shown that patients use more alcohol and coffee than the general population. Surprisingly, males are more likely to have a history of smoking, whereas females smoke less, compared to the general population (21,24). A history of head trauma is more often reported in patients with cluster headache (19,23,25). However, the causality of these associations is uncertain.

Outside attacks, physical examination is normal in the vast majority of patients, except for ptosis or miosis ipsilateral to the headache attacks, which can persist in a minority of patients in the absence of a structural lesion that can cause the symptoms (4). A diagnosis of cluster headache is based on the criteria of the International Criteria of Headache Disorder, third edition (ICHD-3). Contrast-enhanced cerebral magnetic resonance imaging (MRI) should be considered once in every patient, to exclude a causal underlying pathology. A variety of intracranial pathologies have been reported to produce a cluster-like headache phenotype, including cerebral tumours such as prolactinoma or parietal glioblastoma, arteriovenous malformations, and inflammatory conditions (26–28). Repeated contrast-enhanced MRI should be considered if the characteristics of the headache attacks change over time. See **Box 18.2** for a comprehensive differential diagnosis.

Box 18.2 Differential diagnosis of cluster headache

- Paroxysmal hemicrania.
- Short-lasting unilateral neuralgiform headache with conjuncitival injection and tearing (SUNCT).
- Short-lasting unilateral neuralgiform headache with cranial autonomic symptoms (SUNA).
- Migraine.
- Temporal arteritis.
- Trigeminal neuralgia.
- Sinusitis.
- Glaucoma.
- Tumours (particularly parasellar/pituitary).
- Arteriovenous malformations.
- Infarction.
- Dissection of carotid or vertebral arteries.

Pathophysiology

Cluster headache is thought to be a neurovascular disease, in which the so-called trigeminal autonomic reflex can play a role (29). Experimental stimulation of the trigeminal ganglion leads to an increase of intra- and extracerebral cranial blood flow (durovascular complex). The first division of the trigeminal nerve innervates the dura mater. Its neurons project to second-order neurons in the trigeminocervical complex, which consists of the trigeminal nucleus caudalis and the dorsal horns of C1 and C2. Pain signals from the trigeminocervical complex project to the hypothalamus, thalamus, and cortex via pain processing pathways (30–32). The trigeminocervical complex also activates the parasympathetic autonomic outflow, as it projects to the superior salivary nucleus. The superior salivary nucleus gives rise to cranial parasympathetic efferents that traverse along with the facial nerve, passing through structures such as the geniculate ganglion and synapsing in the sphenopalatine ganglia. These neurons project to the cranial vessels and the dura mater, and stimulation results in dilatation of the vessels and irritation of the trigeminal nerve endings (**Figure 18.1**) (31).

The trigeminal nerve endings contain vasodilator peptides like calcitonin gene-related peptide (CGRP), substance P, neuropeptide A, and vasoactive intestinal peptide (VIP) that innervate blood vessels (31). During a cluster headache attack, CGRP and VIP levels increase in cranial venous blood, indicating activation of the trigeminovascular system (33,34).

The hypothalamus is also thought to be involved in the pathophysiology of cluster headache. Diurnal and seasonal rhythmicity of cluster headache suggests involvement of the suprachiasmatic nucleus, also known as the biological clock (35). The suprachiasmatic nucleus projects onto the orexinergic system, which has influence on functions such as feeding, the sleep–wake cycle, and the ability to modulate trigeminal nociceptive processing. Genetic association studies have suggested a role of the orexinergic system (see 'Genetics'), as a polymorphism in the OX_2R receptor (*HCRTR2*) was repeatedly found to be associated with cluster headache (36–38).

In positron emission tomography studies a difference is seen in the hypothalamic grey matter in patients in and outside an active episode of cluster headache (39–41). It has been hypothesized that these hypothalamic volume abnormalities could reflect a dynamic process, which might tend to reverse outside the attack phase.

Genetics

At present, cluster headache is considered to be a complex genetic disorder, i.e. multiple genetic and environmental factors contribute to cluster headache susceptibility. The risk of a first-degree family member of a cluster headache patient also having cluster headache is 5–18 times higher than in the general population, and for second-degree relatives 1–3 times higher (6). *HCRTR2* is so far the only established susceptibility gene for cluster headache (37,42–44). In a genome-wide association study no variant was statistically significant associated with cluster headache (45). The three most suggestive polymorphisms were repeated in a Swedish cohort of cluster headache and controls, but no impact was found on the risk of developing cluster headache in those with these polymorphisms (46).

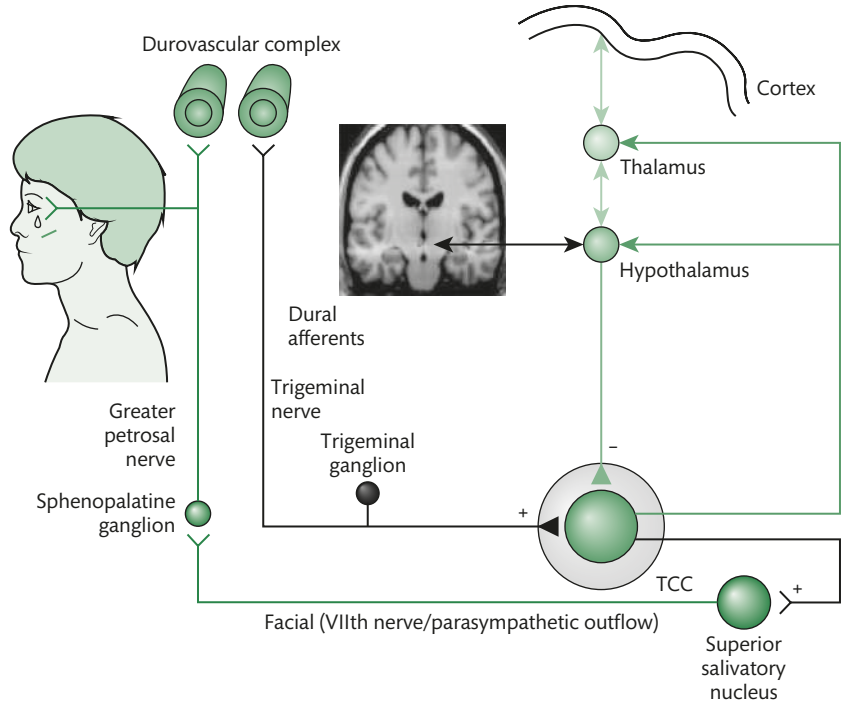

Figure 18.1 (see Colour Plate section) The trigeminal autonomic reflex.

TCC, trigeminocervical complex.

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Diagnosis

A diagnosis of cluster headache is made based on the history of the patient, by applying the ICHD-3 criteria (Box 18.1) (4). Because of the distinct phenotype and the typical annual and circadian pattern, the diagnosis should not pose great problems in typical patients. In daily practice, however, a delay of 3–5 years in making a diagnosis of cluster headache is not uncommon (10,47,48). One of the reasons is that, at first, the symptoms are ascribed to eye, nose, sinus, jaw, or teeth disorders by patients and physicians. Furthermore, the relative rarity and the episodic nature (attacks often disappear spontaneously) also cause difficulty in making the correct diagnosis in time.

Differential diagnosis

Cluster headache is one of the primary headaches categorized as trigeminal autonomic cephalalgias (TACs), which owe their name to the trigeminal distribution of the pain and the accompanying ipsilateral autonomic symptoms. In general, attacks of paroxysmal hemicrania (PH) are shorter than those of cluster headache, but there is an overlap in duration (PH: 2–45 minutes; cluster headache 15–180 minutes) (see Chapter 19). However, in contrast with cluster headache, PH responds dramatically to treatment with indomethacin. Short-lasting unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) can be differentiated from cluster headache by the duration of the attacks. SUNCT and SUNA attacks last between 1 second and 10 minutes, with a median of 1 minute (see Chapter 20).

To differentiate between migraine and cluster headache is sometimes difficult. Two features can be important. Firstly, patients with migraine often seek rest, whereas most cluster headache patients are restless during an attack. Secondly, the duration of a cluster headache attack is 15–180 minutes and that of a migraine attack 4–72 hours. There are, however, exceptions with cluster headache attacks being longer and migraine attacks shorter (especially when treated successfully). Both cluster headache attacks and migraine attacks can be accompanied by nausea, vomiting, photophobia, phonophobia, and osmophobia, but this is more often the case in migraine. Cluster headache attacks can be preceded by aura symptoms, so that this also cannot be used for a definite distinction between cluster headache and migraine. However, cluster headache can be differentiated from migraine in the majority of cases by its frequency and the typical time pattern of attacks.

For a comprehensive differential diagnosis see Box 18.2.

Treatment

The treatment of cluster headache consists of a combination of acute and prophylactic treatment. Approximately 10% of patients with chronic cluster headache, however, do not respond to pharmaceutical prophylactic treatment. In these refractory patients surgical procedures can be considered.

Acute symptomatic treatment

Acute treatment aims at reducing the pain of an individual headache attack. The treatment should act rapidly, because of the severity of the pain and its relatively short duration. The most effective acute

treatments are the 5-$HT_{1B/1D}$ agonist sumatriptan in injectable and intranasal formulations, and inhalation of 100% oxygen.

The first choice is sumatriptan 6 mg subcutaneous (SC). A double-blind, placebo-controlled trial showed that 46% of the patients are pain-free within 15 minutes (49). In the past, patients were advised to use a maximum of two sumatriptan doses per day, but, based on recent case reports and anecdotal experience, a higher number of doses could be allowed if monitored carefully (50).

Sumatriptan nasal spray can also be effective, but is probably of use only in longer attacks (> 45 minutes), because it acts slower than the SC form (51). Oral triptans and oral analgesics, like non-steroidal anti-inflammatory drugs, are not effective in cluster headache, mainly because they act too slowly. Opiate-containing analgesics are also not recommended.

Another option for attack treatment is inhalation of 100% oxygen with a flow rate between 7 and 12 litres per minute for around 15 minutes. It quickly relieves attacks in about 60% of patients, especially in attacks with milder pain (52). In some patients, however, it seems to postpone the attack rather than abort it (53,54).

Intranasal zolmitriptan can be an alternative for patients who do not respond to or cannot tolerate sumatriptan and oxygen. Intranasal zolmitriptan 5 mg, however, is slower than sumatriptan SC. A double-blind placebo-controlled study showed that 38.5% of patients were pain free 30 minutes after zolmitriptan 5 mg. A dose of 10 mg was also effective but caused more side effects than the 5-mg dose (55,56). Remarkably, oral zolmitriptan was also shown to be somewhat effective in attacks of episodic cluster headache, but not in those with chronic cluster headache (57).

There is little evidence for the efficacy of dihydroergotamine (DHE) for individual attacks. An open-label study of 54 patients (episodic and chronic) showed an improvement in patients who were repeatedly treated with intravenous DHE. All patients were headache free after 5 days of treatment (58). DHE is also available in a SC and an intramuscular injectable form.

Prophylactic treatment

The goal of prophylactic treatment is to reduce the number of cluster headache attacks as much as possible. This treatment is given during the bout in patients with episodic cluster headache and continuously in those with chronic cluster headache.

The prophylactic treatment of first choice is verapamil in both episodic and chronic cluster headache (59). It is generally well tolerated and can be safely combined with sumatriptan. In most patients dosages up to 480 mg daily are effective; however, some patients need dosages as high as 960 mg daily. Electrocardiography should be performed at baseline, before every increase in dose and/or annually to check for atrioventricular cardiac block, which is potentially dangerous and thus a contraindication to continuing verapamil treatment (60). The most common side effects of verapamil are constipation, fatigue, dizziness, and bradycardia (61,62).

Lithium was shown to be effective in chronic cluster headache, but it is associated with more side effects than verapamil (61,63). The dose must be based on repeated measurements of the serum level of lithium, which should be between 0.8 and 1.2 mEg/l. Monitoring of renal and thyroid function should be performed on a regular basis. Lithium can cause nausea, vomiting, diarrhoea, tremor, weight gain, and hypo- or hyperthyroidism, especially when taken in high doses (64,65).

Methysergide is often prescribed for cluster headache, although no controlled double-blind studies have been performed. Open studies have shown the benefit of methysergide in 20–73% of patients. The initial dose is 1 mg daily and can be slowly increased (1 mg for 3–5 days) to a maximum of 12 mg daily (66). Methysergide can only be used for a maximum of 6 months, because of the risk of fibrotic complications (lung, retroperitoneal, cardiac valvular) after long-term use (67). After a 'drug holiday' of at least 1 month, the drug can be prescribed again. Unfortunately, the drug is no longer available in Europe or North America.

Topiramate probably has some efficacy. Open-label studies showed a reduction of more than 50% of attacks in 21% of patients. Episodic cluster headache patients tended to respond more often than chronic cluster headache patients. Side effects included dizziness, cognitive and language dysfunction, somnolence, ataxia, paraesthesia, weight loss, and nausea (68–70).

Prednisone was shown to be effective in open-label studies. In a large study, 60 mg prednisone completely prevented attacks in 77% and partially in 12% of patients (71). Prednisone works rapidly, but it can only be used for a short period owing to side effects, and in most cases it will interrupt cluster headache only temporarily and not cause complete remission of the episode. It is therefore mostly used for bridging to long-acting prophylactic treatments.

Other preventive drugs sometimes used for cluster headache are ergotamine tartrate, melatonin, sodium valproate, pizotifen, gabapentin, and baclofen, but evidence of efficacy is limited (64,72–74).

Nerve blocks

Occipital nerve injections containing a mixture of local anaesthetic and corticosteroid were proven to be effective in episodic and chronic cluster headache patients in a randomized controlled trial (RCT). There was a reduction of daily attacks in 95% of group receiving cortivazol, a glucocorticoid, versus 55% in the placebo group. There was no difference in direct treatment effect between the chronic and episodic form of cluster headache (75). In another study in chronic cluster headache patients, attacks recurred 3.5 weeks after injection (76). In episodic patients, however, the effect lasted longer, and even permanently in the majority of patients (76,77). Like oral corticosteroids, treatment with occipital nerve injections is mainly regarded as a therapy to bridge the time necessary to initiate and titrate long-acting prophylactic medications until the right dosage is reached and efficacy is achieved.

Neuromodulation

Unfortunately, a small proportion of chronic cluster headache patients is or becomes intractable or intolerant to medical treatment (78). In these patients different experimental, invasive, non-pharmacological treatments mainly targeting the trigeminal nerve or the cranial parasympathetic outflow tract have been performed (79). Functional imaging studies in cluster headache have identified activations in the region of the posterior hypothalamus, leading to trials of neurostimulation in that area (40).

Hypothalamic deep brain stimulation (DBS) was shown to be effective in some patients with medically intractable chronic cluster headache in small open studies (80). Unfortunately, this treatment can lead to high (even fatal) risks (81–84). Retrospectively,

activation and treatment with DBS was more often located in the midbrain perimesencephalic grey substance than in the hypothalamus (85,86).

DBS, with its risks and sometimes lack of effectiveness, has led several research groups to investigate extracranial invasive treatments, such as occipital nerve and sphenopalatine ganglion stimulation.

Occipital nerve stimulation is shown as effective as DBS in the long term. A recent study in chronic cluster headache reported an improvement of 90% in attack frequency in 80% of patients, but often there is a time delay of several months to reach the optimal effect (87). Several small, open studies also showed promising results of occipital nerve stimulation in medically intractable chronic cluster headache and related headaches (83,88–90). No serious complications were seen. A randomized clinical trial on the effect and safety of occipital nerve stimulation in medically intractable chronic cluster headache is ongoing (91).

The sphenopalatine ganglion is an extracranial structure lying in the pterygopalatine fossa, containing parasympathetic and sympathetic nerves. It is presumed to have a role in cluster headache pathophysiology accounting for the cranial autonomic symptoms during attacks. Intervention procedures including sphenopalatine ganglion blocks and lesions have also demonstrated relief in patients with cluster headache (92). A prospective randomized sham controlled trial in 28 patients with chronic cluster headache showed a reduction of more than 50% of attacks in 12 patients (93).

Vagal nerve stimulation is an invasive neuromodulation therapy that has been used for the treatment of epilepsy and medication-resistant depression. A recent case series reported a decreased frequency and severity of cluster headache after vagal nerve stimulation (94). There is now a non-invasive vagal nerve stimulator device available. An open-label study with this device showed an subjective improvement in 13 of 14 patients; prophylactic treatment could be reduced in seven of the patients (95). In a recent study this non-invasive vagal nerve stimulator (gammaCore®; Electrocore) was evaluated as adjunctive prophylactic therapy for cluster headache attacks in patients with chronic cluster headache (96). Patients with chronic cluster headache (n = 48) treated with this vagal nerve device plus standard care were compared to standard care (n = 49) alone; vagal nerve-stimulated patients had a significantly greater reduction in the number of attacks per week compared with controls. In addition, 40% of those treated with standard of care plus vagal nerve stimulation versus 8.3% treated with standard care showed a reduction of more than 50% in attacks. There were no serious treatment-related adverse events. In two RCTs the effect of non-invasive vagal nerve stimulation as acute therapy was investigated in both episodic and chronic cluster headache (97,98). Vagal nerve stimulation was an effective acute therapy in episodic cluster headache (48% gammaCore® vs 6% sham) (97).

Future treatment options

Monoclonal antibodies directed against the CGRP receptor and molecule have been shown to be effective for the preventive treatment of migraine. As CGRP is elevated during cluster headache attacks, studies are currently underway to evaluate the safety and efficacy of these biologics for both episodic and chronic cluster headache. A first study to determine if CGRP itself induces cluster headache attacks showed that CGRP provokes attacks in active phase episodic and chronic cluster headache, but not during the remission phase in episodic cluster headache (99).

Conclusion

In summary, cluster headache is characterized by unilateral very severe headache attacks lasting 15–180 minutes with ipsilateral autonomic features. Patients are often restless during an attack. The differentiation among other paroxysmal headache syndromes is sometimes difficult. Cranial MRI could be considered in patients to rule out intracranial pathology, which can give rise to a headache phenotype that is indistinguishable from primary cluster headache.

The pathophysiology of cluster headache is not known. The trigeminal autonomic reflex and hypothalamic disturbances are likely involved. Cluster headache is probably a complex genetic disorder.

Treatment consists of a combination of acute and prophylactic treatment. Acute treatment aims at reducing the pain of an individual headache attack. First choices are oxygen and/or sumatriptan SC. Prophylactic treatment aims at reducing the number of cluster headache attacks as much as possible, with verapamil as the drug of first choice. Unfortunately, not all patients respond to the available medical treatment options. For those patients, a range of experimental therapies may offer possible alternatives.

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19

Paroxysmal hemicrania

Clinical features and management

Gennaro Bussone and Elisabetta Cittadini

Introduction

Paroxysmal hemicrania (PH) was initially described by Sjaastad and Dale in 1974 (1) and called 'chronic paroxysmal hemicrania' 2 years later (2). PH is classified as a trigeminal autonomic cephalalgia (TAC) by the International Classification of Headache Disorders, third edition (ICHD-3) (see also Chapter 17) (3,4). The current criteria require at least 20 attacks of severe unilateral orbital, supraorbital, or temporal pain, lasting 2–30 minutes, accompanied by ipsilateral cranial autonomic features such as ptosis, eyelid oedema, conjunctival injection, lacrimation, nasal blockage, or rhinorrhoea. Attacks usually have a frequency of more than five per day, and respond exquisitely to indomethacin.

Epidemiology

Patients with PH have been described in different countries (5–8). The incidence and prevalence of PH has been reported to be about 1–3% that of cluster headache (5), or about 1 in 50,000 (9), although it may be even rarer (10).

Sex distribution

Initially PH was considered to be predominant in females, with a female-to-male ratio of 7:1 (1). However, in a subsequent review of 84 patients the ratio was 2.36:1 (5), and two recent case series (7,11) did not show a clear female preponderance at all. This differs from cluster headache (see also Chapter 18), where there is a clear male preponderance. The sex distribution of PH is more similar to that of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome (see also Chapter 20). The earlier view of PH as a predominantly female condition was probably due to misdiagnosis of male patients with PH as cluster headache (11).

Pathophysiology

The pathogenesis of PH is less well understood than that of other primary headaches, such as migraine (12). Calcitonin gene-related peptide and vasoactive intestinal polypeptide are elevated during PH attacks (13). This release is likely to represent both trigeminovascular and cranial parasympathetic activation, and is similar to what has been observed in patients with cluster headache. The activation of the trigeminal and autonomic systems together seems to be a marker of TACs (14,15). A degree of activation of cranial autonomic response is a normal response to a cranial nociceptive input (16). Useful data to understand more about TACs, and PH in particular, comes from functional imaging studies. Posterior hypothalamus activation contralateral to the pain has been observed in PH, in addition to contralateral activation of ventral midbrain, red nucleus, and substantia nigra (17). Hypothalamic region activation has been also reported in cluster headache (18), SUNCT (19,20), and hemicrania continua (21). In the latter, the ventrolateral midbrain area is also activated (21).Whether the latter region is the key to understanding the therapeutic effect of indomethacin in these disorders remains a relevant question for future research (11).

The cranial autonomic features may be prominent in these syndromes owing to central disinhibition of the trigeminal–autonomic reflex by the hypothalamus (22). There are direct hypothalamic–trigeminal connections (23), and the hypothalamus is known to play a modulatory role on the nociceptive pathways (24). A positron emission tomography study in patients with chronic cluster headache (see also Chapter 18) with hypothalamic deep brain stimulation showed a functional connection between the hypothalamus and the trigeminal system. The hypothalamic stimulation induced activation in the ipsilateral hypothalamic grey at the site of the stimulator tip and the ipsilateral trigeminal system. However, the activation of the trigeminal system did not trigger pain or autonomic cranial features, suggesting that the activation of the trigeminal system is not sufficient to generate pain in cluster headache and perhaps in other TACs (25).

It has been suggested that the posterior hypothalamus area plays a role in terminating the attacks rather than triggering them in cluster headache and the TACs (26).

Recently it has been also argued that hypothalamic activation may not be specific to TACs but just a part of the general central pain network (27). Hypothalamic activation and structural alterations have been also reported in other pain conditions such as migraine (28) and hypnic headache (29) (see also Chapter 26).

In the coming years, further functional neuroimaging and anatomical work studies are required to elucidate more clearly the role of the posterior hypothalamic region in the pathophysiology of TACs in general and PH specifically.

At present it is not known what mechanism of action or interaction with pathophysiological mechanisms is the key aspect to indomethacin's unique pharmacology in indomethacin-sensitive headache, including PH (30). Indomethacin inhibits the production of nitric oxide (NO) by endothelial and inducible nitric oxide synthase (31,32). An animal study (33) showed that indomethacin inhibits NO-induced dural vasodilation, whereas other cyclooxygenase (COX) inhibitors, such as naproxen and ibuprofen, do not. It is possible that NO plays a relevant part in indomethacin's efficacy in PH and hemicrania continua, yet its role still needs to be fully understood.

Clinical picture

Site of pain

According to the ICHD-3 criteria (3), the site of the pain is unilateral, orbital, supraorbital, or temporal. Three separate case series (4,6,10) of PH confirmed that these are the most frequent locations. Yet, the pain can also be distributed elsewhere in the head (10). The pain is strictly unilateral, although a side shift may occur (10).

Autonomic features

The ICHD-3 criteria (3) require at least one cranial autonomic feature with the attacks. Lacrimation, nasal congestion, conjunctival injection, and rhinorrhoea are the most frequent accompanying features (5). However, a wider range of autonomic features has been reported in a large case series such as facial flushing, sense of aural fullness, or of aural swelling (11).

Laterality and severity of the pain

Typically the attacks of PH are side-locked, but five cases of bilateral pain have been reported (34–38). Interestingly, four of these cases had bilateral pain without cranial autonomic features and the possibility has been raised that these indomethacin-sensitive, short-lasting, bilateral headaches without autonomic symptoms represent a novel headache syndrome (39).

Cluster headache (see also Chapter 18) is typically described as an excruciating syndrome and is often called 'suicide headache' (40), yet data from large case series showed that other TACs such as SUNCT/SUNA (41) (see also Chapter 20) and PH are also extremely painful conditions (11).

Duration and frequency of attacks

The current ICHD-3 criteria (3) require that the duration of each attack ranges between 2 and 30 minutes and a that a frequency of more than five attacks per day for more than half of the time is present.

In a prospective study of 105 attacks in five patients (42), the mean attack duration was 13 minutes and the range was 3–46 minutes; the mean attack frequency was 14 attacks in 24 hours and the range was 4–38 attacks.

In a large case series the range of the attack duration was between 10 seconds and 4 hours, with a mean of 17 minutes, although the patients with very short attacks also had longer attacks of several minutes (11). The number of attacks per day in that series was between 2 and 50, with a mean of 11 attacks in 24 hours (11).

Paroxysmal hemicrania and interictal pain

Interictal pain is not a characteristic feature, although it has been reported in case series of patients with PH presented in the literature. In a prospective study, one of eight patients reported tenderness between attacks (43), and 28 of 84 patients in a worldwide retrospective study had interictal discomfort (5). More recently, a large prospective study showed that 18 of 31 patients had background pain (11). Eight (44%) of these 18 patients had medication overuse and 7 (88%) of the 8 patients with overuse had a personal or family history of migraine, or 'headache not otherwise specified'. The remaining 10 patients (56%) had background pain without analgesics overuse, and seven (70%) of them had a personal history positive for headache, either migraine or 'headache not otherwise specified'. The interictal pain was reported to be relatively mild in comparison to the pain of the attacks, and this feature can be used to differentiate these patients from those with hemicrania continua (see also Chapter 21). A retrospective study (7) also showed that eight (47%) patients of 17 had interictal pain, which was intermittent in seven (41%) and continuous in one (6%) patient. The interictal pain was not reported during the early phase of the condition. The comparison of patients with interictal pain with those without was statistically significant in two parameters. Patients with interictal pain had a longer duration of the chronic form (69.0 vs10.7 months; $P = 0.0006$), and the dose of indomethacin required was also higher in patients with interictal pain (187.5 vs 113.9; $P = 0.0018$) (7).

Migrainous features and behaviour

Bilateral phonophobia and photophobia are characteristic symptoms of migraine (3) (see also Chapter 6), yet can occur unilaterally in some patients (44). Unilateral phonophobia and photophobia have been reported to be common in PH, hemicrania continua (45), SUNCT (41,45), and cluster headache (45,46).

In one study of 31 patients with PH (11), 65% of patients had phonophobia and photophobia, and 39% patients had nausea or vomiting during the attacks, or both; phonophobia was unilateral in 25% and photophobia in 40%. In another study (7), 24% of 17 patients had photophobia and 24% phonophobia and at least one

migrainous feature such as nausea, or vomiting, photophobia, or phonophobia was present in 53% of patients.

Agitation and restlessness are typical features of cluster headache (40), and aggressive behaviour has also been also described (see also Chapter 18) (47). It has been described that 62% of the patients with SUNCT are also agitated during attacks (41), and in a case series of 31 patients with PH, 80% of patients were agitated or restless, or both, during attacks and one-quarter reported aggressive behaviour during attacks (11). In a case series of 17 patients with PH (7), 76% had agitation or a sense of restlessness.

Circadian and circannual periodicity

PH attacks occur regularly throughout the day, without a nocturnal preponderance (5,7,11,42,43,48). In contrast with cluster headache, a clear circadian and circannual periodicity has not been reported in patients with PH (7,11).

Triggers

The majority of attacks are spontaneous, but around 10% of PH patients report provocation of attacks by neck movements and in about 7% of patients alcohol provokes attacks (5). Other frequently mentioned triggers are stress and exercise (11).

Periodicity and chronicity

The ICHD-3 criteria (3) classify PH as episodic PH and chronic PH. In the episodic form attacks occur in periods lasting 7 days to 1 year, separated by attack free-periods lasting 1 month or longer. In the chronic form attacks occur for more than 1 year without remission or with remission lasting less than 1 month. About 20% of the patients have the episodic form and the remaining 80% the chronic form (11). This is in contrast with CH where the episodic form is more frequent (see also Chapter 18) (47). The reason of this difference in pattern is not understood.

Secondary paroxysmal hemicrania

Probably as a result of publication bias, a number of cases of symptomatic PH have been reported in the literature, although a causal relationship with the underlying structural lesion is not clear in many of those cases (11). Different pathological processes have been suggested to cause symptomatic PH (48). In side-locked headaches such as (possible) PH, a thorough investigation, including magnetic resonance imaging (MRI), is warranted (49).

Pituitary tumours are often associated with TAC-like phenotypes, but in the largest study investigating this association, no patients with PH were found (50). In that cohort of 84 patients with a pituitary tumour, 5% had SUNCT and 4% cluster headache. However, it is unknown whether the prevalence of pituitary tumours is higher in TAC patients, as no prospective community-based study has been performed to address this issue (51). The precise mechanism underlying pituitary tumour-associated headache is still unknown, although it is likely to be a combination of physical and biochemical tumour characteristics, as well as patient predisposition to headache (52).

Differential diagnosis

Distinguishing PH and cluster headache

A clinical overlap exists between PH and cluster headache (see also Chapter 18). In fact, in both conditions the attacks are strictly unilateral, relatively brief, and associated with ipsilateral cranial autonomic features. At present the absolute response to indomethacin (is the only factor that allows a distinction between these two conditions (3,53–55). Nevertheless, there are some other useful clinical clues. Typically, PH is characterized by (i) shorter duration and (ii) high frequency of attacks. In contrast to PH, cluster headache is characterized by the presence of (i) circadian and circannual periodicity, and (ii) provocation of attacks by alcohol within 1 hour in 90% of patients during cluster bouts (47).

Distinguishing PH and SUNCT

SUNCT attacks are typically shorter, with a range between 5 and 240 seconds (see also Chapter 20) (3), but longer attacks can occur, with attacks lasting up to 600 seconds having been recorded (41). Additionally, another difference with PH is the character of the attacks. In SUNCT, attacks are typically described as single stabs, a group of stabs, or long attacks with a saw-tooth pattern of stabs between which the pain does not return to baseline (41). Most SUNCT attacks are triggered by cutaneous triggers such as touching the face or scalp, washing, shaving, eating, brushing the teeth, talking, and coughing (41,56). In contrast, most PH attacks are spontaneous (5,11), and have a longer duration (11).

Distinguishing PH and trigeminal neuralgia

First-division trigeminal neuralgia (see also Chapter 27) attacks last for 5–10 seconds, with a duration of longer than 30 seconds being rare (57). Prominent conjunctival injection is not present with the pain, although slight lacrimation can sometimes be present (58). Typically, trigeminal neuralgia attacks are precipitated by cutaneous stimuli in the trigeminal territory; a feature that is not characteristic of PH (59).

Distinguishing PH with interictal pain and hemicrania continua

The differential diagnosis between PH with interictal pain and hemicrania continua (see also Chapter 21) can be challenging, and a careful history accompanied with a headache diary is extremely useful during the diagnostic evaluation. The headache diary can provide relevant information regarding temporal aspects of the pain. Some clinical features can also help. In our experience, hemicrania continua typically has less prominent cranial autonomic features than PH. Furthermore, the background pain in hemicrania continua is typically more severe than interictal pain in PH. Painful exacerbations in hemicrania continua are long lasting (usually several hours) and less frequent than the short-lasting and frequent attacks associated with PH (60) (Table 19.1).

Family history

A family history of PH has been described (61). Migraine is described as a genetic headache disorder (62), and mutations have

Table 19.1 Comparison based on large case series of paroxysmal hemicrania, hemicrania continua of cluster headache and SUNCT/SUNA present in literature

	Cluster headache (47)	Paroxysmal hemicrania (11)	SUNCT/SUNA (41)	Hemicrania continua (83)
Sex	3 M:1 F	M = F	1.5 M:1 F	1 M:1.6 F
Pain				
• Quality	Sharp/stabbing/throbbing	Sharp/stabbing/throbbing	Sharp/stabbing/throbbing	Throbbing/sharp/constant
• Severity	Very severe	Very severe	Severe	Moderate/severe/very severe
• Distribution	V1>C2>V2>V3≠	V1>C2>V2>V3	V1>C2>V2>V3	V1>C2>V2>V3
Attacks				
• Frequency (/day)	1–8	11	100	No pattern
• Length (minutes)	30–180	2–50	1–5	30–37 days
				Background pain
Triggers				
• Alcohol	+++	+	−−+++	+
• Nitroglycerin	+++	+		++
• Cutaneous	−	−		−
Agitation/restlessness (%)	90	80	65	69
Phonophobia/photophobia (%)	65	65	25	80
Episodic vs chronic	90:10	35:65	10:90	18:82

SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms; M, male; F, female; ≠ C, cervical and V, trigeminal.

been described in patients affected by familial hemiplegic migraine (see Chapter 10) (63–65). Furthermore, a family history of cluster headache (66) and SUNCT has been described (67). A genetic study of a large group of patients with PH would be important to establish a genetic component, yet this would be a challenge owing to its rarity (11).

Diagnosis

A careful clinical history supplemented with a headache diary, a detailed neurological examination and a trial of indomethacin are needed to make a diagnosis of PH. A brain MRI scan is a reasonable investigation to be performed in all patients with PH.

Natural history

PH can start at any age, even in childhood (68,69). The available data suggest that PH is a lifelong condition, with a mean duration of illness of 13.3 ± 12.2 years (5), although episodic PH can transform into chronic PH and vice versa (5,7,11). Patients can experience long-lasting remissions (11,70). Responses and doses of indomethacin tended to be stable over the time and it is in our practice to re-examine and re-image the brain in patients who stop responding (11). Further, a proportion of patients can decrease the dose of indomethacin required to maintain a pain-free state over time (71).

Treatment

The diagnosis of PH requires an absolute response to indomethacin (54,55). The indomethacin test can be performed in two different ways: an oral trial or a placebo-controlled Indotest test with intramuscular indomethacin (21,54). The oral mean daily dosage is 100 mg, with a range of 25–300 mg, although some patients only need 12.5 mg daily (5,55,72,73). Some two-thirds of patients report side effects at some point, mainly gastrointestinal, which may lead to a discontinuation of the medicine (11). In this context, where gastrointestinal side effects are a problem, employing a placebo-controlled Indotest by injection can be very useful. The parenteral trial consists of a single blind administration of 100 mg or 200 mg versus placebo (11). The placebo-controlled indomethacin test may be a suitable aid in the diagnostic evaluation (11).

Patients who develop gastrointestinal problems, are an important challenge for clinicians. Some patients have responded to COX-2 (selective inhibitors (74–76), although their long-term safety makes this option less attractive (77). Topiramate has been reported to be useful in some cases of PH (78,79).

Most PH attacks are too short to be suitable for acute therapy, although subcutaneous sumatriptan is reported to be useful in selected group of patients with longer attacks (11). Greater occipital nerve injection with lidocaine and methylprednisolone may be helpful in some patients with PH (80), as is non-invasive vagus nerve stimulation (73) . Other (invasive) neuromodulatory procedures, such as blockade of sphenopalatine ganglion, neurostimulation of the posterior hypothalamus, and occipital nerve stimulation, are reserved for refractory PH (72,81,82).

Conclusion

PH is classified as a TAC by the International Headache Society (3). TACs are a group of primary headaches that include cluster headache, PH, and SUNCT/SUNA. They are characterized by strictly unilateral head pain occurring in association with intense cranial autonomic features. PH is characterized by intermediate duration and intermediate attack frequency (4). The exquisite response to indomethacin is the essential criteria for the diagnosis of PH.

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20

SUNCT/SUNA

Clinical features and management

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Introduction

SUNCT syndrome was described in 1978 by Sjaastad et al. (1), and was fully characterized in 1989 under the heading 'short-lasting unilateral neuralgiform headache attacks with conjunctival injection, tearing, sweating, and rhinorrhea' (2). The acronym SUNCT (short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing) was first used in 1991 (3), and summarizes the clinical features of this syndrome. In 2004, this condition was classified in group 3 (trigeminal autonomic cephalalgias (TACs)) of the International Classification of Headache Disorders, second edition (ICHD-2) (4). In the vast majority of reported cases, SUNCT attacks lasted 5–240 seconds and were accompanied by both conjunctival injection and lacrimation. These features were selected as diagnostic criteria at that time, when a conservative and safe position was convenient.

The restrictive diagnostic criteria for SUNCT led to a less restrictive syndrome with the acronym SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic features) (5,6). SUNA was included in the appendix of ICHD-2 (4), along with other novel entities that had to be validated. According to such a proposal, SUNA could be diagnosed with the presence of just one cranial autonomic feature, and the duration of pain attacks was increased up to 10 minutes.

Clinicians familiar with these syndromes have been divided into two groups regarding their nosological view of SUNCT and SUNA. Some authors favour the idea that SUNCT is a subset of SUNA, while others support the idea that both phenotypes are just different expressions of the same condition (7,8). The two clinical pictures clearly overlap. Most recently, the third edition of the ICHD (ICHD-3) has included both SUNCT and SUNA in the same section of the TACs under the heading 'short-lasting unilateral neuralgiform headache attacks' (9). Therefore, SUNCT and SUNA are currently classified as separate subtypes of the same disorder (**Boxes 20.1 and 20.2**).

The clinical pictures

SUNCT

SUNCT syndrome is characterized by short-lived unilateral, orbital or periorbital, painful attacks, with prominent autonomic accompaniments always including both ipsilateral conjunctival injection and tearing (**Box 20.3**). It is a rare disorder, slightly more common in males (male-to-female ratio 1.4:1), with a mean age of onset around 50 years (range 5–88 years) (10–12). A hereditary component may be present in some patients, as there have been two reports of familial SUNCT (13,14).

Symptoms and signs are strictly unilateral, with the pain usually confined to the ocular and periocular area (1–3,10–12). Nearly all patients with SUNCT feel the pain within the trigeminal territory, mostly in the area supplied by the first division of the trigeminal nerve (V1). A spread beyond the midline or co-involvement of the opposite side has occasionally been observed, with the pain still predominating on the originally symptomatic side (10). Exceptional extensions of the pain towards the ear or the occiput, and shifting side attacks, have also been reported (10–12).

SUNCT attacks are usually characterized by moderate or severe pain. An excruciatingly severe pain is not frequent. Pain quality is commonly described as burning, stabbing, or electric (10–12). Alternative descriptions are lancinating, piercing, pricking, pulsating, sharp, shooting, spasmodic, steady, or throbbing (10).

Most SUNCT attacks are triggered by mechanical stimuli acting on trigeminal or extra-trigeminal areas (1–3), while only a minority of attacks seem to be spontaneous. Very few patients have entirely spontaneous attacks, with no triggers. Unlike the paroxysms of trigeminal neuralgia, SUNCT attacks are not followed by a refractory period (2,15–17). Only some exceptional patients diagnosed with SUNCT have apparently had refractory periods (6). SUNCT attacks start and cease abruptly. The solitary attacks usually have a 'plateau-like' pattern (2), but other temporal profiles have also been described (15,16): 'repetitive' (short-lasting attacks in rapid

Box 20.1 Classification of short-lasting unilateral neuralgiform headache attacks

3.3 Short-lasting unilateral neuralgiform headache attacks.

3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT).

3.3.1.1 Episodic SUNCT.

3.3.1.2 Chronic SUNCT.

3.3.2 Short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA).

3.3.2.1 Episodic SUNA.

3.3.2.2 Chronic SUNA.

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succession), 'sawtooth-like' (and its variant 'staccato-like', in which consecutive spike-like paroxysms occur without reaching the pain-free baseline), and 'plateau-like plus exacerbations' (admixture of 1–2-second jabs superimposed on top of the conventional plateau-like pattern) (**Figure 20.1**).

The mean length of SUNCT paroxysms is around 1 minute (2,7), with a usual range of 10–120 seconds, and a total range of 1–600 seconds as stated by the ICHD-3 criteria (9). Objective measurements of 348 attacks in 11 patients rendered a mean duration of 49 seconds, with a range of 5–250 seconds (18). However, the whole reported range extends from 1–600 seconds according to mostly subjective estimations (6). Only very rarely have long-lasting attacks reaching 1–2 hours' duration been observed (19). Such prolonged SUNCT attacks should be taken as rare variants, as even in those patients the vast majority of attacks have a typical length.

Between attacks, the patients are normally free of symptoms. However, sometimes the patients feel a very low-grade background pain or discomfort in the symptomatic area throughout the symptomatic periods (19). This background ache can be rather fluctuating or intermittent.

During active periods, the frequency of attacks may vary from less than one attack per day to more than 30 attacks per hour. The attacks predominate during the daytime; nocturnal attacks are seldom reported (18). The natural course of SUNCT is mostly chronic (6), with attacks occurring for more than 1 year without remission, or with remission periods lasting less than 3 months (9). However, the syndrome may occasionally attain an episodic temporal pattern (6), with attacks occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting 3 months or more (Box 20.3) (9).

Pain attacks are regularly accompanied by prominent, ipsilateral conjunctival injection and lacrimation, with both signs generally appearing in tandem once the attack has started (1,2). The presence of both autonomic signs is a *sine qua non* diagnostic criterion for SUNCT (**Box 20.3**). It is worth noting that lacrimation and conjunctival injection are macroscopically evident a few seconds after the beginning of the pain, and cease just as quickly after the pain stops. In other words, the ocular accompaniments develop in an 'explosive' fashion. Occasionally, SUNCT attacks may be accompanied by either lacrimation or conjunctival injection alone. This may indicate that the lacking autonomic accompaniment was too subtle to be noticed, or that the patient has been observed for too short a period of time to allow for the development of other autonomic features.

Rhinorrhoea and/or nasal congestion are found in approximately two-thirds of patients with SUNCT. Rhinorrhoea takes more time to develop in full, is clinically apparent from the middle part of the attack, and then overlasts the pain by some seconds. In addition, there is subclinical increase of forehead sweating, as well as an increase of

Box 20.2 Diagnostic criteria for short-lasting unilateral neuralgiform headache attacks

3.3 Short-lasting unilateral neuralgiform headache attacks

Description

Attacks of moderate or severe, strictly unilateral head pain lasting seconds to minutes, occurring at least once a day and usually associated with prominent lacrimation and redness of the ipsilateral eye.

Diagnostic criteria

A At least 20 attacks fulfilling criteria B–D.

B Moderate or severe unilateral head pain, with orbital, supraorbital, temporal, and/or other trigeminal distribution, lasting for 1–600 seconds and occurring as single stabs, series of stabs, or in a saw-tooth pattern.

C At least one of the following cranial autonomic symptoms or signs, ipsilateral to the pain:

1 Conjunctival injection and/or lacrimation
2 Nasal congestion and/or rhinorrhoea
3 Eyelid oedema
4 Forehead and facial sweating
5 Miosis and/or ptosis.

D Occurring with a frequency of at least one a day.[1]

E Not better accounted for by another ICHD-3 diagnosis.

[1] During part, but less than half, of the active time course of *3.3 Short-lasting unilateral neuralgiform headache attacks*, attacks may be less frequent.

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Box 20.3 Diagnostic criteria for SUNCT

3.3.1 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT)

Diagnostic criteria

A Attacks fulfilling criteria for *3.3 Short-lasting unilateral neuralgiform headache attacks*, and criterion B below.

B Both of the following, ipsilateral to the pain:

1 Conjunctival injection
2 Lacrimation (tearing).

3.3.1.1 *Episodic SUNCT*

Attacks of SUNCT occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting 3 months or more.

3.3.1.2 *Chronic SUNCT*

Attacks of SUNCT occurring for more than 1 year without remission, or with remission periods lasting less than 3 months.

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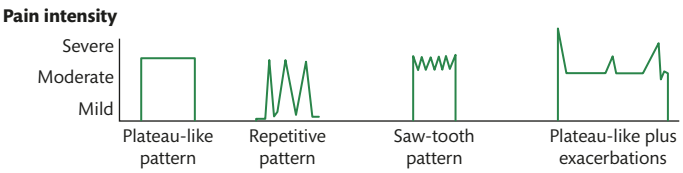

Figure 20.1 Temporal profile of individual SUNCT attacks.

Adapted from *Headache*, 34, Pareja JA, Sjaastad O, SUNCT syndrome in the female, pp. 217–220. Copyright (1994) with permission from John Wiley and Sons.

intraocular pressure and corneal temperature (20), predominating on the symptomatic side.

During periods with a high load of attacks, there may be swelling of the eyelids on the symptomatic side owing to vascular engorgement and oedema (20). This produces a decrease in palpebral width, which is not paretic in nature (pseudoptosis). Otherwise, neither ictal nor interictal states of SUNCT are characterized by spontaneous or pharmacological abnormalities in pupil diameter (21). Only very rarely has miosis been described in patients with SUNCT (22,23).

In addition to the local autonomic accompaniments, SUNCT syndrome is associated with generalized phenomena. During SUNCT attacks, there may be increased systemic arterial blood pressure together with a decrease in heart rate (24). Moreover, patients with SUNCT hyperventilate during the attacks, and less markedly so in between attacks (25).

SUNA

Unlike SUNCT, SUNA has only one or neither of conjunctival injection and lacrimation; otherwise, SUNA may be diagnosed in the presence of one or various autonomic accompaniments (**Box 20.4**). As there is great overlap between the diagnostic criteria for both SUNCT and SUNA, SUNA has been proposed as a broader category of headache that would include SUNCT (5,6).

Pure SUNA is thought to be very rare, even more than SUNCT. It was first described in 2005 in an 11-year-old girl suffering from short, sharp headaches located in the back of the eye, which were consistently associated with profuse ipsilateral tearing, but no conjunctival injection or other autonomic features. No refractory periods could be identified, but the attacks did not really have any precipitating mechanism (5). Since then, additional reports of patients fulfilling the criteria for SUNA have been scarce. To date, only one large series has been published, which included 37 patients with SUNA from multiple centres (26). In that series there were 18 males and 19 females, and the mean age of onset was 45 years (range 15–92 years).

SUNA attacks are similar to SUNCT in location, duration, frequency, and severity. Yet, the site of the pain is more varied in SUNA. Compared with SUNCT, SUNA attacks are more often located in the temple, the side of the head, V2, and V3 (6). Cranial autonomic signs are also more varied in SUNA, without the coupling of conjunctival injection and tearing characteristic of SUNCT. Lacrimation is the most common autonomic feature, followed by nasal blockage or rhinorrhoea. In the case of SUNA, there are more patients who only have spontaneous attacks, although it is also more common for patients with SUNA to have predominantly triggered attacks. As in SUNCT, typical attacks of SUNA are not followed by refractory periods, and this may help to distinguish SUNA from trigeminal neuralgia. Only a small minority of the reported patients had a refractory period after cutaneous triggers (26).

Box 20.4 Diagnostic criteria for SUNA

3.3.2 Short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNA)

Diagnostic criteria

A Attacks fulfilling criteria for *3.3 Short-lasting unilateral neuralgiform headache attacks*, and criterion B below.

B Not more than one of the following, ipsilateral to the pain:
- **1** Conjunctival injection
- **2** Lacrimation (tearing).

3.3.2.1 *Episodic SUNA*

Attacks of SUNA occurring in periods lasting from 7 days to 1 year, separated by pain-free periods lasting at least 3 months.

3.3.2.2 *Chronic SUNA*

Attacks of SUNA occurring for more than 1 year without remission, or with remission periods lasting less than 3 months.

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Aetiology: primary and secondary forms

The aetiology and pathogenesis of SUNCT and SUNA are largely unknown. In the majority of cases these conditions cannot be attributed to another disease, so they are regarded as primary. However, some patients showing similar signs and symptoms have an underlying lesion, and are considered to suffer from secondary forms.

A typical clinical picture of SUNCT has been described in patients with various types of lesions, which have been mostly located in the posterior fossa or the pituitary region (10–12). These lesions comprise tumours, vascular malformations, brainstem infarctions, demyelination, traumatic injuries, herpes zoster and other infections, and congenital abnormalities of the skull (27). Some of these lesions may be incidental findings, but some of them must be related to SUNCT as their suppression may change the clinical course. For instance, the first known symptomatic case of SUNCT was resolved after surgical removal of a cerebellopontine vascular malformation (28). In a series of five patients presenting with SUNCT and an underlying pituitary tumour, three had major improvement after surgery (29); surprisingly, one patient with a pituitary tumour had the onset of SUNCT after radiation therapy (30). Symptomatic SUNA has been associated with the presence of an epidermoid cyst in the cerebellopontine angle (31), vertebral artery dissection (32), cranial trauma (33), and herpes zoster (34). The possibility of underlying causes makes neuroimaging mandatory as part of the diagnostic work-up in both SUNCT and SUNA, preferably with magnetic resonance imaging (MRI) of the brain and MRI-angiography. Interestingly, MRI-dedicated views of the trigeminal nerve root have shown neurovascular compression in a substantial number of SUNCT or SUNA cases, resembling classical trigeminal neuralgia (35). As dedicated views for the trigeminal nerve are not always obtained, the presence of neurovascular compression may be underestimated.

Pathophysiology

SUNCT and SUNA are conceived as TACs, together with cluster headache, paroxysmal hemicrania, and hemicrania continua. TACs are believed to depend essentially on the activation of the trigeminal system, with pain felt in the area supplied by the first division (V1) of the trigeminal nerve, together with a disinhibition of a trigeminofacial brainstem reflex responsible for the oculofacial autonomic accompaniments (36). Although the location of the pain and the autonomic accompaniments are quite similar, TACs differ in the duration, frequency, and temporal

distribution of attacks, as well as the precipitating mechanisms and the response to treatment. Such differences may depend on the origin of the process and/or the modulation of the pain. Likewise, the pain-modulating system appears to behave differently in SUNCT/SUNA and trigeminal neuralgia, as the attacks of SUNCT/SUNA have longer length and are not followed by a refractory period (12–15).

Functional neuroimaging has shown hypothalamic activation during SUNCT attacks (37). Such activation has been claimed to be pathogenically relevant in SUNCT. Indeed, the hypothalamus is anatomically connected to the pain-modulating system and the superior salivary nucleus, and could therefore modulate both the pain and the autonomic accompaniments. Alternatively, the hypothalamus could lead to a permissive stage for the attacks to occur, or just function as a relay station for increased neuronal inputs. Hypothalamic activation is not exclusive to SUNCT, and has actually been observed in all the TACs (38–40).

Treatment

As the attacks of SUNCT and SUNA are very short lasting, there are no abortive therapies for individual attacks. The aim of therapy is to prevent or suppress the occurrence of attacks.

No medication is consistently effective for SUNCT or SUNA (41–46). Given the rarity of these conditions, most available data come from observational studies, case series, and case reports. To date, only one small placebo-controlled trial of topiramate has been performed in patients with SUNCT, with no definite results (26). Yet, a substantial number of the reported patients with SUNCT or SUNA have seemed to benefit from certain pharmacological and non-pharmacological procedures.

Preventive treatments for SUNCT and SUNA include lamotrigine, gabapentin, and topiramate. Lamotrigine is the drug of choice for the long-term preventive treatment of SUNCT (46–53). It should be initiated at 25 mg daily and gradually titrated, guided by response and side effects. Lamotrigine has been the most commonly administered prolonged treatment in patients with SUNCT and, when compared to other therapies, has a higher odds of responders (53). Nevertheless, treatment with lamotrigine has not been as effective in patients with SUNA (26). Gabapentin may be also effective for both SUNCT and SUNA (26,54–57). Topiramate is effective in some patients with SUNCT, but has not shown a reliable effect on SUNA (26). Carbamazepine has shown effectiveness in some patients with SUNCT or SUNA. However, it is not recommended as a first-line treatment as there is a lack of response in the majority of patients (26). Zonisamide, oxcarbazepine, eslicarbazepine, and pregabalin have been apparently effective in individual cases (26,58–60). The effect of verapamil is uncertain (26,61). There is a report of a patient with refractory SUNCT responding to clomiphene (62).

Both intravenous lidocaine (26,63–65) and intravenous phenytoin (66) can be useful as transitional treatments during severe exacerbations of SUNCT while appropriate preventive therapy is being implemented or just to give the patients some temporary relief. In one case report the positive effect of lidocaine lasted for 2 months (64). Oral or intravenous corticosteroids have also suppressed severe bouts of SUNCT attacks in a number of cases (67,68). However, not all patients have responded to these therapies.

Greater occipital nerve blocks with local anaesthetics (26,69) and superior cervical ganglion blockade with opioids (70) have been reported as temporally or partially effective in a few patients. Additionally, peripheral nerve blocks of the supraorbital and infraorbital nerves provided a long-lasting remission in a pregnant patient (71). Likewise, two patients had sustained relief after botulinum toxin A injections distributed over the symptomatic area (72,73). Owing to the scarcity of reports, the results of these procedures should be taken as preliminary.

Surgical procedures have also been tried in the treatment of medically refractory SUNCT or SUNA. For instance, some patients have improved with microvascular decompression of the trigeminal nerve (Janetta procedure) (35,74–76), while others have obtained some benefit with ablative procedures directed to the trigeminal nerve and the sphenopalatine ganglion (percutaneous balloon compression, radiofrequency thermocoagulation, glycerol rhizolysis, or stereotactic radiosurgery) (77–80). Nevertheless, these interventions do not provide compelling results in all cases. In recent times, both peripheral and central neurostimulation techniques (occipital nerve stimulation, and deep brain stimulation in the posterior hypothalamus) have been apparently successful in a few medically intractable cases (81–86).

Nosology

SUNCT is a descriptive condition. Descriptive syndromes consist of those observable features by which they are standardly recognized. For clinical and research purposes, operational definitions must be drawn up from descriptive definitions. Operational definitions (i.e. diagnostic criteria) identify the boundaries between a given condition and similar entities. Researchers must select the best combination of symptoms that are necessary to establish the diagnosis. Therefore, diagnostic criteria of a given condition cannot represent the clinical profile in full, but a practical way to differentiate similar conditions. A distinction of SUNCT from trigeminal neuralgia (see Chapter 27) may be difficult at times (87,88).

Conjunctival injection, lacrimation, and rhinorrhoea were present in 100%, 95%, and 63%, respectively, of the first 21 patients with SUNCT(10). As conjunctival injection and lacrimation were present in nearly 100%, both features were considered essential for the diagnosis of SUNCT. By the time the ICHD-2 diagnostic criteria of SUNCT were established, there was a need to differentiate SUNCT from V1 trigeminal neuralgia. Studies on V1 trigeminal neuralgia had shown that attacks might rarely be accompanied by lacrimation *without* conjunctival injection (89). Otherwise, the duration of trigeminal neuralgia attacks was considered to range between 'a few seconds to a few minutes'. Therefore, SUNCT attacks accompanied by lacrimation could have been difficult to differentiate from V1 neuralgia with lacrimation. Including the co-occurrence of conjunctival injection and lacrimation as a *sine qua non* diagnostic criterion would strengthen the difference with V1 trigeminal neuralgia. Later on, objective duration of V1 neuralgia attacks was assessed (90), thus providing a key feature for the differentiation between SUNCT and V1 neuralgia accompanied by lacrimation (**Figure 20.2**). Accordingly, the initial, conservative diagnostic criteria of SUNCT could have been changed for polythetic criteria, as established for the other TACs. In fact, all three TACs seem to exhibit similar autonomic features.

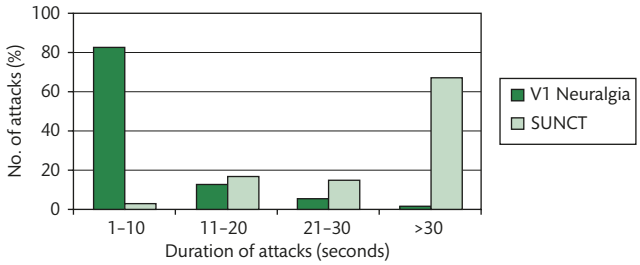

Figure 20.2 Objective measurement of duration of attacks in SUNCT and V1 neuralgia.

Adapted from *Cephalalgia*, 25, Pareja JA, Cuadrado ML, Caminero AB et al., Duration of attacks of first division trigeminal neuralgia, pp. 305–308. Copyright (2005) © SAGE Publications.

The ICHD-2 diagnostic criteria for SUNCT contained only two autonomic features: conjunctival injection and tearing. The two items were connected with 'and' and not with 'and/or'. It was also stated in a note in the appendix that these criteria might be incorrect, and that only one of the two cardinal features might be present. This problem could have been solved by changing 'and' for 'and/or'. Instead, a broader and more inclusive concept is currently represented in the clinical picture of SUNA.

Admittedly, SUNCT is a rare condition, so the definition of SUNCT may have been incomplete on the basis of the first cases observed at the time the diagnostic criteria were settled. Nowadays, the clinical picture of SUNCT is vastly known, including variations in the typical features and presence of atypical features. The descriptions of SUNCT and SUNA are rather similar. Minor differences between those descriptions may partly be due to slight variants of the same disorder. The two clinical pictures largely overlap, thus indicating that both phenotypes could represent complementary clinical pictures of the same syndrome. SUNA has been proposed as a broader category that would include SUNCT, but with the same level of certainty or uncertainty SUNA could also be regarded as the whole clinical spectrum of SUNCT, i.e. typical, atypical, and *fruste* forms

The ICHD-3 kept the restrictive diagnostic criteria for SUNCT, and added SUNA in the same subgroup of TACs as a different phenotype (9). Both clinical pictures have been classified under the nosological structure of short-lasting unilateral neuralgiform headache attacks (**Box 20.1**). For the time being, ICHD-3 has clarified the taxonomy of these related conditions, providing physicians with a practical distinction between SUNCT and SUNA.

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21

Hemicrania continua

Johan Lim and Joost Haan

Introduction

Hemicrania continua (HC) is an uncommon primary headache disorder characterized by continuous, unilateral cranial pain of moderate intensity, more painful exacerbations with cranial autonomic features, and an absolute response to indomethacin (1–5). The unilateral autonomic features and indomethacin responsiveness, besides the overlap in functional brain imaging, are shared with some of the other trigeminal autonomic cephalalgias (TACs), such as episodic and chronic paroxysmal hemicrania (2,6). Hence, HC has recently been grouped under the TACs in the International Classification of Headache Disorders, third edition (ICDH-3) by the Headache Classification Committee of the International Headache Society (**Box 21.1**) (1).

Sjaastad and Spierings were the first to name the condition HC, in their report on two cases in 1984: a 63-year-old woman and a 53-year-old man with continuous, unilateral pain, which had a dramatic response to indomethacin (7). Subsequently, nearly 200 cases of HC have been reported from various countries and ethnic backgrounds (2,8–13, 18).

Epidemiology

The incidence and prevalence of HC are unknown (18). Reported numbers vary considerably: while some authors describe the condition as not rare (10), the relatively limited cases over the years (nearly 200 reported in approximately 30 years) and experience from clinical practice from tertiary referral sites suggest that HC is a rare condition (2). However, a possible publication bias, an ongoing discussion about its clinical features, and a lack of population-based epidemiological studies influence these numbers.

Mean age of onset is reported to be in the third decade, but the condition may begin at any age (2,13). The duration of the illness before diagnosis has been reported to be 5 years, on average, ranging from 6 weeks to 19 years (14).

A small female preponderance, with reported ratios of 1.8:1–2.4:1, has been described (2,8,10).

Clinical picture

HC typically presents with unilateral pain (right and left sides being equally affected) without side shifting (2,5,15). Only a few patients with alternating headache have been reported (2,16–18).The pain is mostly located in the temporal (82%), orbital (67%), frontal (64%), retro-orbital (59%), or occipital/parietal (54%) regions, or at the vertex/peri-orbitally (51%) (2). However, any part of the head or neck can be affected (2,19).

The pain is described as throbbing by a majority, while sharp and continuous pain are also reported frequently. The intensity of the background pain is generally described as moderate, whereas the exacerbations are mostly described as severe (2).

The temporal pattern of HC is characterized by daily and continuous pain, generally without pain-free periods for more than 3 months (1). Two types of HC have been described: firstly, an episodic/remitting form with pain-free periods (without treatment) of at least 1 day; and, secondly, a chronic/unremitting form with daily and continuous pain for at least 1 year, without remission periods of at least 1 day (1,2). Evolution from the remitting to the unremitting form, and vice versa, have been reported (2).

Most patients suffer from an unremitting form, of which the majority is unremitting from onset (2). The average duration of unremitting HC is 12 years, with a range from 3 to 49 years. The interval to progress from remitting to unremitting HC is 8 years, on average, varying from 2 weeks to 26 years.

No clear circadian or circannual preponderance has been described (2).

Exacerbations are daily in about half of the patients, and between one and five times a week in the majority of the remaining half. Cases without exacerbations have also been reported (2). The length of exacerbations varies considerably, from minutes to months.

Exacerbations can both be triggered or occur spontaneously. Commonly reported triggers are the use of alcohol, irregular sleep, stress, and relaxation after stress (2). About half of the patients have improvement of pain after applying heat around head and/or neck and/or staying in a warm environment, whereas a variety of other maneuvers or positions do not seem to have significant effect on the headache (2).

Box 21.1. International Headache Socity diagnostic criteria for hemicrania continua

A Unilateral headache fulfilling criteria B–D.
B Present for > 3 months, with exacerbations of moderate or greater intensity.
C Either or both of the following:
  1 At least one of the following symptoms or signs, ipsilateral to the headache:
    (a) conjunctival injection and/or lacrimation
    (b) nasal congestion and/or rhinorrhoea
    (c) eyelid oedema
    (d) forehead and facial sweating
    (e) forehead and facial flushing
    (f) sensation of fullness in the ear
    (g) miosis and/or ptosis.
  2 A sense of restlessness or agitation, or aggravation of the pain by movement.
D Responds absolutely to therapeutic doses of indomethacin.[1]
E Not better accounted for by another ICHD-3 diagnosis.

Hemicrania continua, remitting subtype

A Headache fulfilling criteria for *Hemicrania continua*, and criterion B below.
B Headache is not daily or continuous, but interrupted (without treatment) by remission periods of > 24 hours.

Hemicrania continua, unremitting subtype

A Headache fulfilling criteria for *Hemicrania continua*, and criterion B below
B Headache is daily and continuous for at least 1 year, without remission periods of > 24 hours.

Probable hemicrania continua

A Headache attacks fulfilling all but one of criteria A–D for hemicrania continua.
B Not fulfilling ICHD-3 criteria for any other headache disorder.
C Not better accounted for by another ICHD-3 diagnosis.

[1] In an adult, oral indomethacin should be used initially in a dose of at least 150 mg daily and increased, if necessary, up to 225 mg daily. The dose by injection is 100–200 mg. Smaller maintenance doses are often employed.

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While at least one cranial autonomic feature during pain exacerbations is required for the diagnosis of HC following the ICDH-3 criteria (1), cases of phenotypically HC-like, indomethacin-responsive headaches without autonomic features have been reported (2). Lacrimation (73%), nasal congestion (51%), conjunctival injection (46%), ptosis (40%), facial flushing (40%), and rhinorrhoea (38%) are most frequently described (2).

Moreover, a majority of patients are agitated during exacerbations, showing restlessness and verbal aggression, but—in contrast to cluster headache—in HC this is not a part of the diagnostic criteria (2). Some patients have reported vague ocular discomfort preceding exacerbations (20). Concomitant primary stabbing headache is present in a third of patients (2). Most patients also end up with migrainous features, such as phonophobia, photophobia, osmophobia, motion sensitivity, and nausea or vomiting, rendering the distinction from migraine and chronic migraine difficult in some (2).

A family history of HC has been reported once, but specific genetic studies have not been carried out (2). A majority of patients have a history of migraine and a family history of migraine. In a few cases, abnormal findings on neurological examination are found, which mainly consist of mild sensory changes in the cranial areas affected by pain (2). Radiologic investigations/magnetic resonance imaging (MRI) are mostly normal, whereas the abnormalities that are found are mostly considered incidental or nonspecific (2,21).

Pathophysiology

While both peripheral and central components have been discussed as relevant for the pathophysiology of HC, a combination of a central component predominating in the primary form and a peripheral component predominating in the secondary form has been argued (22).

Firstly, activation of the trigeminal nerve and the craniofacial parasympathetic nerve in a trigeminal–autonomic reflex seems to play an important role (6). The trigeminal–autonomic reflex consists of a brainstem connection between the trigeminal nerve and facial parasympathic nerves; activation results in pain (exacerbations) and autonomic symptoms, respectively (6). Moreover, stimulation of the trigeminal ganglion is thought to increase extra- and intracerebral blood flow due to a vasodilator response via the parasympathetic outflow (23,24) and propagate local release of calcitonin gene-related peptide, substance P, and parasympathetic (vasoactive intestinal peptide) marker peptides (23).

Also, data from functional MRI and neurophysiological studies have raised the hypothesis that activation of the contralateral posterior hypothalamic grey seems crucial (25): its central permissive functions as pain modulator and/or terminator possibly determine variation in attack duration and phenotypic expression of the pain (26).

Furthermore, anatomical and physiological investigations in rats have shown direct two-way connections between the two aforementioned systems: the trigeminal nucleus caudalis and posterior hypothalamus, which are connected through the trigeminohypothalamic tract (27).

The pathological activation of the trigeminofacial brainstem reflex and posterior hypothalamic grey are shared with some of the other TACs, along with clinical characteristics (e.g. response to indomethacin, unilaterality of pain, and autonomic features), thus suggesting a common biological basis (6). Pontine activation in HC, similar to migraine, may explain the frequent occurrence of migrainous features in this syndrome.

Aetiology: primary and secondary cases

The aetiology of HC is unknown and, as such, HC is considered a primary headache. However, symptomatic, cases have been reported in association with pituitary abnormalities, after vitreous haemorrhage, trauma, carotid dissection, and after cranial surgery (2,12,28). Most authors stress the likelihood of a coincidental association of HC and stated abnormalities in these cases (2,14).

Diagnosis

HC should be considered in patients with continuous unilateral pain of varying intensity accompanied by autonomic features. History and physical examination should not suggest any other headache diagnosis. Exclusion of other pathology with full neuroradiological investigation is recommended. A headache diary may prove helpful to assess headache features accurately.

Possible cases should receive an adequate trial of indomethacin (29), for an absolute response to indomethacin is considered to be the hallmark of HC. Indeed, absolute indomethacin responsiveness is a diagnostic criterion for HC (1). However, some patients with (otherwise) phenotypically classic HC-like headaches, do not respond to indomethacin (29–31).

A positive response to indomethacin is defined as an absolute response within 48 hours. However, a trial of up to 2 weeks is recommended before abandoning the treatment as ineffective. In an adult, oral indomethacin should be at least 150 mg daily (1,32). Pain should promptly recur if indomethacin is stopped (33). Escalating doses or loss of efficacy should be treated with suspicion, as for secondary forms or misdiagnosis (6,34).

Symptomatic HC should be considered in all patients with atypical complaints and those with abnormalities at neurological examination. To consider an underlying lesion as cause of HC complaints, there must be a close temporal relationship between the onset of pain and the onset of the associated lesion, the site of the pain, and the site of the lesion should be in concordance, and—ideally—improvement of the HC symptoms should be achieved after (surgical or other) treatment.

Other TACs with background pain are important considerations in the differential diagnosis of HC (2). In contrast to other TACs, the continuous and moderate nature of the background pain (6) and relatively mild nature of the autonomic features (33) are typical for HC. Exacerbations in HC are longer lasting (several hours to days) and less frequent than in paroxysmal hemicrania (< 10 minutes, many times a day) or cluster headache (15 minutes–3 hours). Also, patients with HC are, on average, younger than patients with chronic paroxysmal hemicrania (14). However, differentiating HC from other TACs might prove difficult, especially when facing chronic paroxysmal hemicrania or cluster headache with interictal pain.

Differentiating HC from (chronic) migraine can also be complicated, as HC frequently presents with migrainous features and exacerbations can resemble migraine attacks. Migraine attacks may also be associated with cranial parasympathetic features. The prevalent autonomic symptoms and 'unilaterality of photophobia and/or phonophobia' are mentioned as features possibly to be used in the distinction between HC and migraine (2).

Medication overuse is diagnosed in three-quarters of patients with HC at some point during the course of their disease. Most patients with HC do not show improvement after medication withdrawal (2).

Treatment

By definition, pain in HC has an absolute response to indomethacin (1,35). The median needed dose is 175 mg, ranging from 50 to 500 mg, but the dose–response relationship has not been systematically explored (2). Some patients can be maintained on lower doses and pain eradication on the lowest possible doses should be attempted, considering the negative effects of its possible long-term usage (36). Generally speaking, there is no response to non-steroidal anti-inflammatory drugs (NSAIDs) other than indomethacin (2,14).

The underlying mechanisms of indomethacin effectiveness are unknown, but recent studies have hypothesized prostaglandin synthesis inhibition via cyclooxygenase (COX) and modulation of autonomic signalling in the sphenopalatine ganglia, possibly through a nitric oxide-mediated pathway as possible mechanism (37,38).

The main side effects of indomethacin are dizziness and gastrointestinal symptoms (e.g. abdominal pain, nausea/vomiting, diarrhoea, and abdominal bloating) (2). Therefore, addition of proton pump inhibitors is advised as it may reduce NSAID-induced gastrointestinal toxicity (39). Furthermore, while most patients do not seem to develop secondary headache due to extended indomethacin use, a subgroup is prone to developing bilateral headache in the context of indomethacin use (2).

Non-indomethacin NSAIDs and other analgesics have often been tried in cases of indomethacin intolerance (mostly because of gastrointestinal side effects), but their efficacy is limited (40). Anecdotal evidence of some efficacy exists for gabapentin (41–43) and melatonin (44–46), the latter also as add-on to indomethacin (47). With respect to their relatively good safety profile, some authors recommend their use in cases of indomethacin intolerance (36). The same authors advise caution when using selective COX-2 inhibitors (although they have also shown to be somewhat effective in individual cases) and opioids for reasons of cardiovascular risks and risk of dependency/addiction. Valproic acid has been used with unclear efficacy (48).

Small series have shown that topiramate and glucocorticoids might prove useful alternatives for indomethacin as prophylactic treatment in some cases (2). Anaesthetic blocks are reported to be effective in half of patients (49–51). Botox was also described as a potential treatment option in HC (52).

Occipital nerve stimulation (ONS) has been shown to be a safe and effective treatment in small series, also in the long term (53), although some authors have seen a varying response in practice (35,36,54,55). ONS is realized by a subcutaneously implanted neurostimulation device with a pulse generator placed in the chest wall/abdomen, which is connected to extension leads with electrodes that stimulate the occipital nerves. Effect is expected within days to weeks; thus, neuroplasticity might be a mechanism. Most commonly reported complications are lead migration, infection, and sensory symptoms due to overstimulation (53). Radiofrequency ablation of C2 or sphenopalatine ganglion gave long-term improvement in some patients (56).

Prognosis

The natural history of HC has not yet been systematically investigated. While HC seems to be, by and large, a chronic condition, some cases of definitive pain resolution after indomethacin discontinuation have been described (57). Indomethacin therapy is not thought to have disease-modifying effects, but it enables most patients to be pain-free and lead normal lives (58).

Conclusion

HC is characterized by continuous unilateral cranial pain of moderate intensity, more painful exacerbations with cranial autonomic features, and an absolute response to indomethacin.

It is considered a primary headache, but possible secondary forms, mostly post-traumatic, have been reported. Activation of the trigeminal–autonomic reflex and the contralateral posterior hypothalamic grey, resulting in pain (exacerbations) and autonomic features, respectively, are thought to play an important role in the pathophysiology of HC.

The incidence and prevalence are not known, but HC is generally regarded as an uncommon disorder. The mean age of onset is in the third decade, with a small female preponderance (female-to-male ratio 2:1).

HC can be divided into a remitting and an unremitting type; most patients suffer from the unremitting variant. The pain is (by definition) side-locked and mainly described as throbbing. Exacerbations, which can occur both spontaneously and be triggered, are accompanied by unilateral autonomic symptoms and sometimes by migrainous features. Physical and supplementary investigations are by and large normal. Other TACs and migraine are the main differential diagnostic alternatives.

Indomethacin has an absolute therapeutic effect on the headache, which can be used for the differential diagnosis. Lowest possible effective doses should be used to minimize negative effects of its possible long-term usage. Dizziness and gastrointestinal symptoms are the main side effects of indomethacin. Hence, the addition of proton pump inhibitors is advised as it may reduce NSAID-induced gastrointestinal toxicity. Non-indomethacin NSAIDs are generally not effective. More investigation is needed regarding relatively new invasive techniques, such as ONS.

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22

Cluster tic syndrome and other combinations of primary headaches with trigeminal neuralgia

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Cluster tic syndrome: cases reported in the literature

In 'cluster tic syndrome', the word 'cluster' refers to cluster headache and 'tic' to 'tic douloureux', a term previously used for trigeminal neuralgia (see also Chapter 27). The term 'cluster tic syndrome' was introduced in 1978 in an abstract (1). In this abstract the headaches were very briefly described as having features of both cluster headache and trigeminal neuralgia, but it is not clear whether the author described two different types of attacks within one patient, or that the attacks had features of both cluster headache and trigeminal neuralgia ('mixed' attacks) so that an unequivocal primary headache diagnosis was not possible. Since then, the term 'cluster tic' has been used in different ways in the literature, but less often to describe these 'mixed' attacks.

Most of the time, however, it is used for the ipsilateral co-occurrence of attacks of cluster headache and trigeminal neuralgia within the same patient, although the two components may appear asynchronously. Since 1978, 39 patients have been described under the diagnosis cluster tic syndrome (Table 22.1); 18 male patients and 17 females (sex was not mentioned for four patients), with an age at onset between 20 and 78 years (1–15). In all cases described, trigeminal neuralgia attacks were ipsilateral to the attacks of cluster headache. This could point to a possible pathophysiological link (see 'Pathophysiology', or a publication bias as attacks occurring at different sides of the face could have been regarded as unrelated and coincidental. These 39 patients can be divided into cases described as having co-occurrence of cluster headache and trigeminal neuralgia (according to the International Classification of Headache Disorders, third edition (ICHD-3) criteria) (n = 24) and a separate entity consisting of (additional) attacks resembling, but not fulfilling all criteria of cluster headache and trigeminal neuralgia (n = 15) (Table 22.1).

Eight cases of 'secondary' cluster tic were described (Table 22.1); in three patients the cluster tic syndrome resolved by treatment of a pituitary adenoma, prolactinoma, or epidermoid in the sella turcica, and in another patient the headaches decreased after venous decompression of the trigeminal nerve (12,13,16,17). In another patient the cluster tic syndrome appeared to be related to multiple sclerosis (18). Basilar artery ectasia and a dural carotid–cavernous fistula were suggested as underlying cause in two other patients (11,19). In a young child a pontine tumour was the underlying cause (14).

In the majority of published patients (n = 39) (Table 22.1), however, there was no obvious structural lesion explaining the headache syndrome, although—especially in the older studies—one could wonder whether brain imaging was sufficient to rule out such a lesion with certainty. Besides, in most patients with cluster tic syndrome a specific magnetic resonance imaging/magnetic resonance angiography to investigate the presence of a vascular compression of the trigeminal nerve root nerve was not performed (20).

Pathophysiology

Some authors question the existence of cluster tic syndrome as a separate entity, because sharp, short pain attacks accompanying the usual longer attacks in cluster headache are often described and should not receive a separate diagnosis (10). Mulleners and Verhagen (9) reject cluster tic syndrome as a separate entity, illustrated by the description of a patient suffering from a pain syndrome consisting of anatomical and temporal characteristics of trigeminal neuralgia with the periodicity of cluster headache attacks. The authors emphasize that, apparently, there are overlapping pain syndromes for which it is not practical to make new diagnostic entities.

Among those who think of cluster tic syndrome as a separate syndrome, different pathophysiological mechanisms have been proposed. Firstly, it was suggested that trigeminal neuralgia and cluster headache only co-occur by chance (3). Secondly, some believe that attacks of cluster headache and trigeminal neuralgia are caused by the same underlying pathophysiological mechanism (4,5,7). This is based on the assumption that the concurrence of two rare disorders, such as cluster headache and trigeminal neuralgia, in the same individual, and synchronously occurring on the same side, is more than coincidental.

Table 22.1 Descriptions of the cluster tic syndrome in the literature.

Reference	Number	M/F	Age at onset
Cluster tic as described in ICHD-3 criteria: co-occurrence of cluster headache and trigeminal neuralgia			
Diamond et al., 1984 (8)	1	0/1	28
Watson and Evans, 1985 (6)	5	3/2	28–76
Donnet et al., 2012 (42)	1	0/1	53
Pascual and Berciano, 1993 (7)	1	1/0	27
Klimek, 1987 (4)	1	1/0	51
Solomon et al., 1985 (10)	4	2/2	19–40
Maggioni et al. 2009 (34)	1	0/1	40
Monzillo et al., 2000 (5)	5	3/2	49–78
Haan et al., 2011 (3)	3	2/1	60–72
Kinfe et al., 2015 (22)	1	1/0	49
Bernal Sanchez-Arjona et al., 2009 (15)	1	1/0	64
Total	24	14/10	28–78
Reference	**Number**	**M/F**	**Age at onset**
Cluster tic described as separate entity consisting of (additional) attacks resembling, but not fulfilling all the criteria of cluster headache or trigeminal neuralgia			
Green and Apfelbaum, 1978 (1)	4	NM	NM
Mulleners and Verhagen, 1996 (9)	1	0/1	45
Alberca and Ochoa, 1994 (2)	10	4/6	20–66
Total	15	4/7	20–66

Reference	Number	M/F		Age at onset
Secondary cluster tic				**Lesion/underlying disease**
Leone et al., 2004 (16)	1	1/0	46	Pituitary adenoma
González-Quintanilla et al., 2012 (18)	1	1/0	29	Multiple sclerosis
Ochoa et al., 1993 (19)	1	1/0	NM	Basilar artery ectasia
Payán et al., 2012 (11)	1	0/1	69	Dural carotid–cavernous fistula
Levyman et al., 1991 (12)	1	0/1	39	Epidermoid tumour sella turcica
van Vliet et al., 2003 (14)	1	0/1	1	Pilocytic astrocytoma pons
Favier et al., 2007 (13)	1	1/0	31	Prolactinoma
de Coo et al., 2017 (17)	1	0/1	41	Venous compression trigeminal nerve
Total	8	4/4	1–69	

M, male; F, female; NM, not mentioned.

The mechanism behind it is, however, still unknown. Thirdly, it is asserted that the cluster tic syndrome is a separate entity consisting of three types of attacks; trigeminal neuralgia attacks, cluster headache attacks, and mixed attacks. A single lesion affecting the trigeminal sensory pathway with involvement of both myelinated and unmyelinated fibres is hypothesized to be the underlying mechanism (2).

Treatment of the cluster tic syndrome

The third edition of the ICHD (ICHD-3) mentions cluster tic syndrome as a note in the cluster headache section (21). It defines cluster tic syndrome as the co-occurrence of trigeminal neuralgia and cluster headache, and advises that these patients should receive both diagnoses, because these two types of attacks each need separate treatments. No randomized clinical trials have been performed in cluster tic syndrome, because of its rarity. In the case reports described (Table 22.1), a variety of medication has been tried with variable success. In most cases carbamazepine was effective for trigeminal neuralgia and often verapamil, lithium, or methysergide for cluster headache. As in cluster headache or trigeminal neuralgia in daily practice, now and then, different kind of medications, dosages, and combinations had to be tried before the attacks ceased. In the literature, some patients are described in whom medication was not effective and who underwent surgical procedures (decompression, section, or thermocoagulation of the trigeminal nerve or root), and these procedures were described to be often effective for both trigeminal neuralgia attacks and cluster headache attacks (2,6,10). However, attacks of cluster headache could eventually reappear after initial relief of both cluster headache and trigeminal neuralgia after trigeminal nerve decompression (2,10). One patient with the cluster tic syndrome was described who responded to cervical non-invasive vagal nerve stimulation (22).

Even more rare conditions: paroxysmal hemicrania tic and other 'tic combinations'

Since 1993, 11 patients have been described with a combination of paroxysmal hemicrania and trigeminal neuralgia, called paroxysmal hemicrania tic syndrome (Table 22.2) (23–28). Most of them were women (nine women, two men), with an age of onset between 40 and 69 years. In three patients an underlying disease was described: a Chiari I malformation and an ecstatic vertebrobasilar junction/basilar artery in close proximity to the left trigeminal nerve root entry zone, and in the third patients the headaches were described as being a clinically isolated symptom, according to the McDonald criteria (27,29–31). As in cluster tic syndrome, in most patients a combination of two treatments was necessary, most of the time a combination of indomethacin and carbamazepine. In one patient the attacks of paroxysmal hemicrania were not responsive to indomethacin, which contradicts the diagnosis of paroxysmal hemicrania, according to ICHD-2 criteria. However, in this patient a combination of carbamazepine and acetazolamide was effective. Three patients in whom trigeminal neuralgia co-existed with paroxysmal hemicrania and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) have been described (32,33). The authors suggested a pathophysiological relationship between these three short-lasting headaches. This was also the case for a

Table 22.2 Descriptions of chronic paroxysmal hemicrania tic syndrome in the literature

Reference	Number	M/F	Age at onset	
Paroxysmal hemicrania tic as described in ICHD-2 criteria: co-occurrence of paroxysmal hemicrania and trigeminal neuralgia				
Hannerz, 1993 (23)	1	0/1	43	
Caminero et al., 1998 (24)	1	0/1	67	
Zukerman et al., 2000 (25)	3	0/3	47–56	
Martinez-Salio et al., 2000 (26)	1	1/0	52	
Boes et al., 2003 (27)	1	1/0	52	
Sanahuja et al., 2005 (28)	1	0/1	69	No relief from indomethacin
Secondary paroxysmal hemicrania tic	**Number**	**M/F**	**Age at onset**	**Lesion/underlying disease**
Monzillo et al., 2007 (29)	1	0/1	51	Chiari I malformation
Boes et al., 2003 (27)	1	0/1	58	Ecstatic vertebrobasilar junction/basilar artery
Ljubisavljevic et al., 2017 (30)	1	0/1	40	Hyperintense lesion in the right trigeminal main sensory nucleus and root inlet and right corticospinal tract at the medulla oblongata
Total	11	2/9	40–69	

M, male; F, female.

combination of trigeminal neuralgia, SUNCT, and cluster headache, as described by Maggioni et al. (34).

As with cluster tic, ICHD-3 mentions paroxysmal hemicrania tic syndrome in a note to the criteria (21). It is defined as the co-occurrence of trigeminal neuralgia and paroxysmal hemicrania, and also in these patients the advice is to give them both diagnoses, because these two types of attacks each need separate treatments (21).

The combination of SUNCT and trigeminal neuralgia has also been described in four case reports (Table 22.3) (35–38). Some authors hypothesize that SUNCT may be modified trigeminal neuralgia, suggesting a single pathological condition (36). Others, however, state that discrimination between first division trigeminal neuralgia and SUNCT is feasible by the presence of autonomic signs at the start of a SUNCT attack, unlike in trigeminal neuralgia in which, if present, these autonomic symptoms are secondary to the head pain (35,39). SUNCT may have been mistaken for trigeminal neuralgia when not fully developed, particularly in the initial stages (*forme fruste,* i.e. with less marked autonomic features) (40).

We found one prospective controlled study giving a hazard ratio for trigeminal neuralgia in migraine to be 6.72 (95% confidence interval 5.37–8.41; $P < 0.001$). The authors conclude that migraine is a previously unidentified risk factor for trigeminal neuralgia (41).

Table 22.3 Descriptions of SUNCT tic syndrome in the literature

Reference	Number	M/F	Age at onset	Lesion/underlying disease
Bouhassira et al., 1994 (36)	1	1/0	53	
Sesso et al., 2001 (35)	1	0/1	56	
Secondary SUNCT tic				
Eguia et al., 2008 (37)	1	0/1	46	Meningitis
Lambru et al., 2017 (38)	1	1/0	58	Medullary infarction
Total	4	2/2	46–58	

SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; M, male; F, female.

Conclusion

Cluster tic syndrome and other combined tic syndromes are very rare and heterogeneously described as case reports in the literature. Three types of cluster tic syndromes can be distinguished: (i) simultaneously occurring trigeminal neuralgia and cluster headache according to the ICHD-3 criteria (most frequent) (21); (ii) attacks not fulfilling criteria for either cluster headache or trigeminal neuralgia but having features of both; (iii) secondary cluster tic syndrome. Trigeminal neuralgia can also co-occur with paroxysmal hemicrania (paroxysmal hemicrania tic) and with SUNCT. In case of co-occurrence of two primary headache syndromes, separate treatments aimed at the two headache syndromes is recommended. The pathophysiology of the tic combination syndromes is unknown.

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PART 4

Other primary short-lasting and rare headaches

23. **Primary stabbing headache** *215*
Rashmi B. Halker, Esma Dilli, and Amaal Starling

24. **Cough headache** *220*
Julio Pascual and Peter van den Berg†

25. **Exertional and sex headache** *225*
Shih-Pin Chen, Julio Pascual, and Shuu-Jiun Wang

26. **Hypnic headache** *230*
Dagny Holle and David W. Dodick

27. **Cranial neuralgias and persistent idiopathic facial pain** *237*
Aydin Gozalov, Messoud Ashina, and Joanna M. Zakrzewska

28. **Some rare headache disorders, including Alice in Wonderland syndrome, blip syndrome, cardiac cephalalgia, epicrania fugax, exploding head syndrome, Harlequin syndrome, lacrimal neuralgia, neck–tongue syndrome, and red ear syndrome** *248*
Randolph W. Evans

23

Primary stabbing headache

Rashmi B. Halker, Esma Dilli, and Amaal Starling

Introduction

Primary, or idiopathic, stabbing headache was first described in 1964 by Lansche in a patient with migraine and stabbing paroxysms as 'ophthalmodynia periodica' (1). Various terms have been used to describe primary stabbing headache (PSH), including ice pick headache (2), sharp short-lived headache (3), jabs and jolts syndrome (4), and idiopathic stabbing headache (5–7). In this review, we will discuss the epidemiology, clinical features, differential diagnosis, pathophysiology, treatment, and prognosis of PSH.

Epidemiology

The reported prevalence of PSH varies widely in the currently available studies. Gender and comorbidity with other headache disorders seems to affect the prevalence.

Two population-based studies reported a prevalence of 0.2–2%. (8,9). In a cross-sectional study of a tertiary neurology clinic in China, the prevalence rate of 'pure' PSH (exclusion of other primary headaches disorders) was reported to be 1.5% (10). In Spain, a retrospective review performed in a specialty clinic found only 33/100,000 patients with PSH with a mean age of onset of 47.1 years (5). However, the Vågå study, performed in Norway (a large-scale cross-sectional study), reported a PSH prevalence of 35.2%, with a mean age of onset of 28 years (11,12). In a prospective study of 725 patients at a tertiary headache clinic, PSH (based on International Classification of Headache Disorders (ICHD)-2 criteria) was reported in 36 patients (5%), with a mean age at onset of 34.1 ± 2.9 years (range 10–72 years) (13). It is unclear why the prevalence data, ranging from < 1% to approximately 35%, has such a wide range, but it is possible that changes in diagnostic criteria (see **Box 23.1**) and selection bias in studies performed in specialty clinics were contributing factors.

In the adult population, PSH is more common in women. The Vågå study demonstrated a female-to-male ratio of 1.49:1 (11). The retrospective review in Spain found a female-to-male ratio of 6.6:1 (5). In a prospective study, where 36 of 725 patients at a tertiary headache clinic were diagnosed with PSH, 26 were females and 10 were males (2.6:1) (13).

PSH also occurs in the paediatric headache population. In a retrospective review of 548 children and adolescents from a paediatric headache clinic, Fusco et al. (14) reported 23 patients (4.2%) with brief (a few seconds to 15 minutes) attacks of self-limited stabbing headache suggestive of PSH. There does not appear to be a sex difference in children with PSH (15,16).

PSH is commonly associated with other headache disorders, including migraine and cluster headache (3,17). PSH was found in 12.6% of all headache patients in a Turkish study (18). This was a higher prevalence than found in general population-based studies (8,9), but lower than in the migraine population (19), who followed 280 migraine patients for a 12-month period, noted a high prevalence of PSH. They found that 40.4% of their migraine patients presented with idiopathic stabbing headache, with a female-to-male ratio of 3:1. Raskin and Schwartz (3) compared the incidence of PSH in 100 migraineurs and 100 control subjects. Three of the 100 control subjects reported episodes consistent with PSH on at least an annual basis. In contrast, 42 of the 100 migraineurs reported similar episodes, with more than 50% of them experiencing the sharp painful episodes more than once a month. In this study, 45% of the paroxysms of ice pick pain were unifocal at the temple or orbit with 69% of the patients having concurrent headache such as migraine superimposed on the paroxysmal ice pick-like pain. Patients with cluster headache have also reported paroxysms of sharp pain consistent with PSH and unique from cluster headache attacks. In an observational study of 33 patients with cluster headache, 11 had paroxysms of pricking or stabbing sensations in the eye, forehead, and upper jaw (17).

In a clinical series, the incidence of PSH was 33/100,000 per year, while in a population study prevalence was found to be 35.2% (5). The mean age of onset of PSH is 23–47 years, with a female predominance in adults and no clear female predominance in children. The prevalence of PSH reported in the literature has varied as a result of reporting bias, particularly as PSH is commonly associated with other headache disorders.

Clinical features

PSH is characterized as paroxysmal attacks of moderate-to-severe stabbing/sharp pain occurring spontaneously in irregular patterns

Box 23.1 Clinical characteristics

Spontaneous/sporadic attacks/irregular pattern
Sharp or stab
1–10 seconds in duration (mean 2 seconds)
Unilateral > bilateral
Moderate to severe

(Box 23.1). Typically, the jabbing pain lasts 1–10 seconds, with two-thirds of patients having moderate-to-severe pain of < 1 seconds' duration (20). Piovesan et al. (19) studied PSH in 280 patients with migraine. In this study the mean duration of pain was 1.42 seconds (1 second in 72.4% of patients, 2 seconds in 18.1%, 3 seconds in 6.3%, 4 seconds in 1%, and 5 seconds in 2%).

The single burst of pain or brief repetitive volleys of pain is similar to an ice pick, needle, or nail jab. In the Vågå population study of PSH, 68% of the 627 jab cases had single jabs, 4% had volleys, and 28% had a mixture of volleys and singlets. Most individuals had experienced only few jabs (11).

The frequency of the attacks can range from one attack per year to 50 attacks daily (20), in a random distribution throughout the day and night in 84%. Chronic occurrence with > 80% attack days per year have been reported in 14% of patients.

Unilateral location has been reported in 59–91.4% of patients.

Paroxysmal stabbing pain occurring in multiple dermatomes has been reported in a prospective study of 28 patients with recurrent stabbing headache. These patients fulfilled the ICHD-2 diagnostic criteria for PSH, except for area of involvement (21).

The pain was originally considered to be in the first branch of the trigeminal nerve and in previous studies 45–62% of patients with PSH reported a purely V1 distribution of pain (5,22). However, more recent studies report that up to 70% of patients have extra-trigeminal (occipital, nuchal, parietal) stabbing pain from nerves innervated by C2–C4 (22); therefore, the ICHD-3 has removed the criterion requiring stabs to be limited to a V1 distribution (see Table 23.1) (23,24).

Unlike trigeminal autonomic cephalalgias (TACs), there are no cranial autonomic features such as tearing or ptosis associated with the attacks of pain. Nausea, vomiting, and photophobia are uncommon; however, accompanying symptoms have been reported in 15–22% (10,22). Although similar findings have been reported in paediatric studies, in one paediatric study, vertigo, nausea, photophobia, and phonophobia have been reported to occur in as high as 47% of children with stabbing headache (25).

Table 23.1 Diagnostic criteria for stabbing headache

International Classification of Headache Disorders, third edition (ICHD-3) diagnostic criteria for primary stabbing headache	
A.	Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B and C
B.	Each stab lasts for up to a few seconds.
C.	Stabs occur with irregular frequency, from one to many per day.
D.	No cranial autonomic symptoms.
E.	Not better accounted for by another ICHD-3 diagnosis.

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PSH is commonly associated with other headaches disorders such as migraine. In a study by Fuh et al. (22), 25% of patients with PSH also had migraine. Migraine was less common in patients who had PSH onset after the age of 50 years (14% vs 38%; $P = 0.02$) than those who first experienced PSH before the age of 50. There appears to be a spatial and temporal relationship to the migraine and stabbing headache as 88% of patients reported an overlap between the location of the migraine and stabbing pain, and 79% of patients reported stabbing pain during a migraine attack (26).

In most patients, there are no triggers for the paroxysmal stabbing pain. However, a few patients reported provocative factors. These triggers included physical exertion, head motions, rapid alterations in posture, physical exertion, bright light, and head motion during migraine attacks (3,26). Ammache et al. (27) reported a case of complete vision loss ipsilateral to the pain in a man with idiopathic stabbing headache, but the patient also had a history of migraine with aura.

PSH is rarely reported in the paediatric population. In a retrospective study in a paediatric neurology service in Saudi Arabia, five children were identified over a 12-year period with PSH, according to the ICHD-2 criteria. Three children had occipital location of their attacks (28). In a retrospective study by Fusco et al. (14), the mean age of onset of stabbing headaches was 9 years, with bilateral distribution in 60% and an orbital or temporal location in 60% of patients (14). This predominant bilateral distribution of pain in the paediatric population is also seen in paediatric migraine patients.

Differential diagnosis

The differential diagnosis of PSH consists of all short-lasting stab-like headaches, primary and secondary. As with the diagnosis of all headache disorders, first an underlying cause for the headache must be ruled out. Several cases of a secondary headache with stabbing-type of pain have been described in the literature, including vascular, autoimmune, infectious, and neoplastic aetiologies (29).

Short lasting, stab-like headaches have been described in both haemorrhagic and ischaemic stroke. Six of the series of 90 patients described a de novo short-lasting, stabbing pain following a haemorrhagic stroke (30). Paroxysmal sharp pain lasting 1–2 seconds has also been described after an acute thalamic haemorrhage in an elderly patient (31). In a prospective series of > 2000 patients with acute ischaemic stroke, 20% of the patients who presented with headache at onset of their stroke described a stabbing headache (32). In another case series, eight patients with stabbing headaches had unilateral or bilateral transverse sinus stenosis on magnetic resonance venogram (33).

In a retrospective review of 20,534 patients, 26 patients fulfilled the ICHD-2 diagnostic criteria of stabbing headache and had underlying autoimmune disorders, including multiple sclerosis, Sjögren's syndrome, systematic lupus erythematous, Behçet's disease, autoimmune vasculitis, and antiphospholipid antibody syndrome (34). Stabbing headache has also been reported with giant cell arteritis (35). Ergün et al. (36) reported that in relapsing remitting multiple sclerosis, stabbing headache (27.8%) was the most common headache in the relapse phase. Klein et al. (37) reported stabbing headache as a sign of relapses in multiple sclerosis.

Stabbing headache has been reported as the presenting symptom of a herpes zoster meningoencephalitis (38). The patient presented to the emergency department with complaints of stabbing pain in the right frontal and temporal head regions. Physical examination was significant for herpetic lesions on her right chest, as well as neck stiffness and cognitive dysfunction. Further work-up confirmed herpes zoster meningoencephalitis. Treatment with aciclovir resulted in resolution of the stabbing head pain.

Stabbing headache has also been the presenting manifestation of intracranial meningiomas (39).

Once secondary headaches have been considered and ruled out, there are multiple primary headache disorders that are included in the differential diagnosis for PSH. PSH and other primary headache disorders can be differentiated by determining the location, triggers, duration of attacks, and the presence or absence of cranial autonomic features.

The TACs including short unilateral neuralgiform headache with conjunctival injection and tearing (SUNCT) should be considered (see also Chapter 20). However, by definition, the TACs including SUNCT must have unilateral cranial autonomic features. The presence or absence of autonomic symptoms is a key feature that will differentiate a TAC from PSH.

Trigeminal neuralgia is a unilateral disorder characterized by brief electric shock-like attacks of pain limited to the distribution of one or more divisions of the trigeminal nerve (see also Chapter 27). The attacks of pain are often precipitated by mechanical stimulation such as speaking, eating, or brushing teeth. The distribution of pain and provocative factors differentiate trigeminal neuralgia from PSH.

Primary cough headache (see also Chapter 24), primary exertional headache, and primary headache associated with sexual activity (see also Chapter 25) are differentiated from PSH mainly by the presence or absence of provoking factors.

Pathophysiology

The pathophysiology of PSH is unknown. Theories include irritation of peripheral branches of the trigeminal nerve or other cranial nerves, and/or intermittent dysfunction of central pain processing that results in spontaneous synchronous discharges or hyperexcitability of neurons. The ephaptic impulses are postulated to travel to the corresponding nerve distribution with the sensation of stabbing pain. Selekler and Komsuoglu (26) proposed that the rationale for stabbing pain to occur commonly in areas of the patient's migraine was the segmental disinhibition of central pain pathway leading to increased susceptibility to 'afferent volley of impulses' (26). Because PSH is more common in patients with migraine, the trigeminal vascular system may play a role, but further studies are required to determine the pathogenesis and pathophysiology of PSH. Other theories include inflammation or focal demyelination within the brainstem in patients with secondary stabbing headache associated with autoimmune disorders (34), although no such finding has been reported in a patient with PSH. Montella et al. (40) suggested that PSH was dural sinus stenosis-associated.

Investigations

Neuroimaging, consisting of either computed tomography or magnetic resonance imaging of the brain, is reasonable in patients presenting with stabbing headache, given that intracranial meningiomas can be a potential secondary cause (39). In elderly patients who present with new-onset headache, additional work-up for secondary causes is important, as there have been cases of thalamic haemorrhage and giant cell arteritis presenting with stabbing headache (31,35).

Treatment

In patients with infrequent attacks, the explanation that PSH is a benign condition can be sufficient and treatment may not be necessary. Patients with frequent attacks might require intervention. Acute treatment is not practical given the short duration of the attacks. Consequently, only prophylactic medication can be considered.

PSH, like several other primary headache conditions, is considered indomethacin-responsive. While it is not clear why indomethacin is so effective and therefore the treatment of choice for these disorders, there is evidence that indomethacin has a few unique properties, particularly compared with other non-steroidal anti-inflammatory drugs (NSAIDs). Indomethacin has been shown to inhibit nitric oxide release, as well as decrease cerebral blood flow and lower cerebrospinal fluid pressure. NSAIDs in general, including indomethacin, reduce inflammatory pathways by inhibiting cyclooxygenase and phosphodiesterase (41). Individuals with PSH have been reported to respond quickly to indomethacin ranging from 75–250 mg/day given in divided doses.

Long-term indomethacin use is often limited owing to gastrointestinal and renal side effects. There are other options for patients who are unable to tolerate indomethacin or have a contraindication to its use. Piovesan et al. (42) presented three patients with PSH who derived a complete therapeutic response to celecoxib 100 mg q12h, respectively, within 3 days, 6 days, and 14 days of starting treatment. O'Connor et al. (43) reported on an 88-year-old woman with PSH who responded to etoricoxib 60 mg daily, with complete cessation of attacks within a week. Rofecoxib 25 mg q12h for 10 days decreased attack frequency by 50% (44). Etoricoxib and rofecoxib are not available in the USA owing to safety concerns. Indomethacin is not Food and Drug Administration-approved for children < 15 years old. Although there is little literature available about the use of indomethacin in PSH, a trial of indomethacin is recommended by Myers and Smyth (45) in children with severe paroxysmal pain without autonomic symptoms in whom secondary causes have been ruled out.

Melatonin (3–12 mg), nifedipine 90 mg, and gabapentin 400 mg q12h have also been reported to be effective in isolated cases (44,46,47).

Onabotulinum toxin A (BoNTA) was studied in a prospective, unblinded study in 24 patients with PSH (48). The area of stabbing pain was classified based on location (orbital, frontal, temporal, parietal, and occipital), and patients received 5 units of BoNTA into each area where they experienced the stabs. Because many patients

had more than one attack zone, the mean dose of BoNTA used was 11.81 ± 7.17 units. Two patients did not experience any benefit from the injections, but the remaining 22 saw improvement, with three individuals noting complete remission. The benefit from BoNTA lasted approximately 63 days. As no patients reported any side effects, BoNTA may be a reasonable therapeutic option for PSH.

Prognosis

Although there have not been any prospective studies on PSH prognosis, it is generally considered a benign condition, and may remit with time. Periodic medication tapering trials to evaluate for the possibility of remission is reasonable.

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24

Cough headache

Julio Pascual and Peter van den Berg[†]

Introduction

Headaches related to exertion can be brought on by Valsalva manoeuvres ('cough headache'), prolonged exercise ('exercise headache'), and sexual excitation ('sexual headache') (1). These conditions are a challenging diagnostic problem. They can be primary or secondary, and their aetiologies differ depending on the headache type. Historically, cough headache has been included in the broader context of exercise-induced headache, but clinical features of cough headache are clearly different from those of exertional and sexual headache, which do have many properties in common (2) (see also Chapter 25).

Tinel, in 1932, reported several patients with intermittent, paroxysmal headaches following exertion and manoeuvres that increased intrathoracic pressure (3). In the 1950s, Symonds called the disorder 'cough headache' and demonstrated that it may be a benign syndrome without demonstrable cause (4). Before this report, cough and exertional headaches were always considered ominous symptoms, and there was no clear recognition that benign types of these headaches existed. The first large series published on exertional headache or head pain related to exertion came from the Mayo Clinic. This work, however, still combined all exercise-induced headache, which contributed to the lack of differentiation among these provoked subtypes and included the following statement: 'in every patient with this complaint, an intracranial lesion of potentially serious nature, such as a brain tumour, aneurysm or vascular anomaly, has been suspected; and even when no such lesion could be identified, an uneasy uncertainty usually remained' (5). It was not until modern neuroimaging techniques became available that these activity-related headaches were clinically differentiated.

In the International Classification of Headache Disorders (ICHD), cough headache is included within 'Other primary headaches' and defined as headache precipitated by coughing or straining in the absence of an intracranial disorder. New ICHD-3 IHS diagnostic criteria are given in **Box 24.1** (6).

Epidemiology

Cough headache has been classically considered a rare entity (7). However, Rasmussen and Olesen (8) have shown that the lifetime prevalence of cough headache is 1% (95% confidence interval 0–2). Over 10 years, of the 6412 patients who attended a general neurology department, 68 (1.1%) consulted because of cough headache (9,10).

Aetiology

Headache precipitated by cough can be either a primary benign condition or secondary to structural intracranial disease. From case series prior to computed tomography and magnetic resonance imaging (MRI) it was concluded that about 20% of patients with cough headache had structural lesions, most of them a Chiari type I malformation (3,5,11,12). However, with modern neuroimaging techniques it is clear that about 40% of patients with cough headache have secondary cough headache due to tonsillar descent or, more rarely, to other space-occupying lesions in the posterior fossa/foramen magnum area (13). Up to one-third of patients with Chiari type I malformation experience headache aggravated by Valsalva manoeuvres, mainly cough (14). Therefore, it can be concluded that about 60% of the patients with cough headache will show no demonstrable aetiology, while 40% will be secondary to structural lesions, mostly at the foramen magnum level.

Pathophysiology

The pathophysiology of secondary cough headache is reasonably well understood. This headache seems to be secondary to a temporary impact of the cerebellar tonsils below the foramen magnum (15–18). In two patients with cough headache and tonsillar herniation, Williams (15) demonstrated a pressure difference between the ventricle and the lumbar subarachnoid space during coughing. This pressure difference, called cranio-spinal pressure dissociation, displaced the cerebellar tonsils into the foramen magnum. Williams also observed that the headache disappeared after decompressive craniectomy. Nightingale and Williams described four more patients who had headache due to episodic impact of the cerebellar tonsils in the foramen magnum after abrupt Valsalva maneuvers (17). Data from Pascual et al. (13,14) support the concept that tonsillar descent is the actual cause of cough headache. Furthermore, it was also shown that the presence of cough headache in Chiari type

[†] It is with regret that we report that Peter van den Berg died on 26 January 2019.

Box 24.1 Diagnostic criteria for primary cough headache

- At least two headache episodes fulfilling criteria B–D
- Brought on by and occurring only in association with coughing, straining and/or other Valsalva manoeuvre
- Sudden onset
- Lasting between 1 second and 2 hours
- Not better accounted for by another ICHD-3 diagnosis.

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I patients correlated with the degree of tonsillar descent (13,14), although this was not supported by findings of Sansur et al. (18).

Alterations in posterior fossa cerebrospinal dynamics in symptomatic patients with Chiari type I with abnormal pulsatile motion of the cerebellar tonsils have been described (19,20). Such movement produced a selective obstruction of the cerebrospinal fluid (CSF) flow from the cranial cavity to the spine. The amplitude of the tonsillar pulsation and the severity of the arachnoid space reduction were associated with cough headache (20). These data confirm that symptomatic cough headache is secondary to Chiari type I deformity and that this pain is due to compression or traction of the causally displaced cerebellar tonsils on pain-sensitive dura and other anchoring structures around the foramen magnum innervated by the first cervical roots.

In contrast to secondary cough headache, the pathophysiology of primary cough headache is not known. The possibility of a sudden increase in venous pressure being sufficient itself to cause headache due to an increase in brain volume has been proposed (21). There should be other contributing factors, however, such as a hypersensitivity of some receptors, sensitive to pressure, hypothetically localized on the venous vessels (22). One of the potential aetiologies for this transient receptor sensitization could be a hidden or previous infection. Interestingly, Chen et al. (23) have found that patients with primary cough headache are associated with a more crowded posterior cranial fossa, which may be a further contributing factor for the pathogenesis of this headache syndrome. A recent study using magnetic resonance venography showed a transverse or jugular vein stenosis in five of the seven patients with primary cough headache. However, the question remains if and how is the stenosis related to primary cough headache (24).

Clinical manifestations

Primary cough headache is defined as head pain precipitated by coughing or other Valsalva manoeuvres in the absence of any intracranial disorder. According to the ICHD-3 criteria (Table 24.1), primary cough headache is a sudden-onset headache lasting from 1 second to 30 minutes, brought on by and occurring only in association with coughing, straining, and/or Valsalva manoeuvres (6).

The clinical picture of primary cough headache is somewhat characteristic, which should allow its differentiation from secondary cases (12,13,14,24–26). It usually affects those over the age of 40 years, with a mean age in patient series above 60 years of age. There is a slight male predominance. The pain begins immediately or within seconds of the precipitants. Such precipitants include coughing, sneezing, nose blowing, laughing, crying, singing, lifting a weight, straining at stool, and stooping. Prolonged physical exercise is not a precipitating factor for primary cough headache. The pain is moderate to severe in intensity, with a sharp, stabbing, splitting, or even explosive quality. The headache is usually bilateral but can be unilateral. The pain is most often in the occipital region, but may also be in the frontotemporal regions. According to the criteria the headache should last from 1 second to 30 minutes, but usually lasts seconds to several minutes. In some patients, a dull, aching pain follows the paroxysm for several hours (27). Primary cough headache is not associated with other clinical manifestations, not even nausea or vomiting, photo- and phonophobia, and responds to indomethacin (13,14). Primary cough headache is an episodic disease, ranging from 2 months to a maximum of 2 years in our experience.

Differential diagnosis

Cough headache can be either a primary benign condition or secondary to structural intracranial disease (**Figure 24.1**). By definition, primary cough headache can only be diagnosed if neuroimaging studies are normal. The presence of a Chiari type I malformation or any other lesion causing obstruction of CSF pathways or displacing cerebral structures must be excluded before cough headache is assumed to be benign (**Figure 24.2**). Around 30% of patients with Chiari type I malformation experience headache aggravated by Valsalva manoeuvres, mainly cough. Cough headache can be the only clinical manifestation of Chiari type I malformation for several years in about one-fifth of symptomatic patients (10,13). However, most if not all patients with symptomatic cough headache finally develop posterior fossa symptoms or signs, mainly dizziness/vertigo, unsteadiness, and syncope.

Several clinical clues may be helpful in differentiating between primary and secondary cough headache. Secondary cough headache usually begins earlier in life, is located more in the occipital region, is associated with fossa posterior symptoms, and does not respond to indomethacin. However, studies have showed a response to indomethacin in some patients with secondary cough headache (28).

Differential diagnosis with primary exertional headache is straightforward. Exertional headache is not brought on by Valsalva manoeuvres, but by prolonged physical exercise (see also Chapter 25). In addition, contrary to primary cough headache, primary exertional headache is typical in young people (< 50 years of age) and contains a lot of migrainous characteristics. Primary sexual headache shares a lot of properties with exertional headache (see also chapter 25) (10,13). Sexual intercourse is a prolonged exercise with Valsalva manoeuvres; therefore, an orgasm can also be seen as precipitating factor for 'exertional' headache in some patients (29).

Migraine, cluster headache, post-lumbar puncture headache, and idiopathic intracranial hypertension can be aggravated, but not elicited, by cough. Cough headache can also be symptomatic of low CSF pressure (see Chapter 38) (30). These patients complain of both orthostatic and cough headaches. These are related to either a reversible pseudo-Chiari due to brain sagging which can be seen on the MRI (**Figure 24.3**) (31), or cerebral venous sinus engorgement and cerebral venous hypertension. Given the differential diagnosis outlined, every patient with cough headache should have an MRI of the brain to rule out a posterior fossa lesion, and MRI with gadolinium to rule out dural enhancement associated with CSF leak and intracranial hypotension. In spite of scattered reports, there is not enough scientific background to support unruptured aneurysms

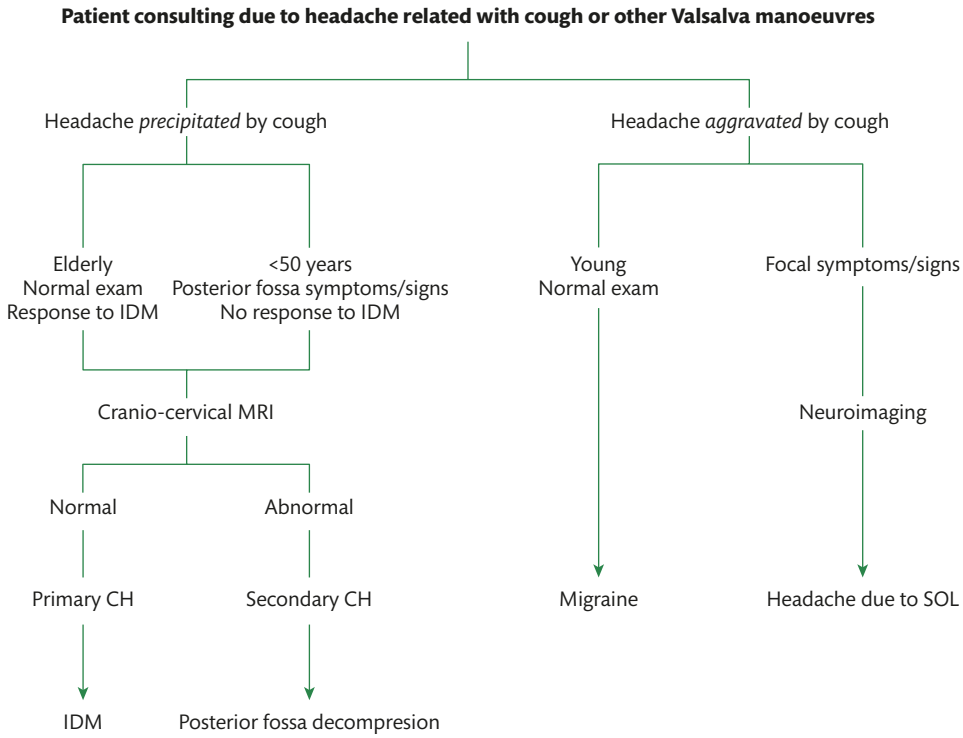

Figure 24.1 Differential diagnosis and management of patients consulting for headache related to cough.
IDM, indomethacin; MRI, magnetic resonance imaging; CH, cough headache; SOL, space-occupying lesion.

(32) or carotid stenosis (33,34) as specific causes for cough headache. Therefore, a magnetic resonance angiography study is not mandatory in these patients.

Treatment

Symptomatic treatment is not practical because of the short duration and multiplicity of cough headaches. Potential precipitants, for instance lung infections or cough-inducing medications, must be treated or withdrawn. Most patients with primary cough headache respond to indomethacin, given prophylactically at doses usually ranging from 25 to 150 mg daily (25,35,36). The mechanism of action of this drug is unknown, but could include a decrease in intracranial pressure (37). This would explain the benefits seen with lumbar puncture or acetazolamide in some patients with primary cough headache (21,22,38). There is no consensus on treatment duration with indomethacin. However, two studies show that after good

Figure 24.2 (a) Cranial magnetic resonance imaging (MRI) of a patient consulting for cough headache showing slight tonsillar descent. (b) Cine-MRI confirms that this Chiari type I malformation makes the circulation of cerebrospinal fluid difficult, mainly posteriorly (arrows).

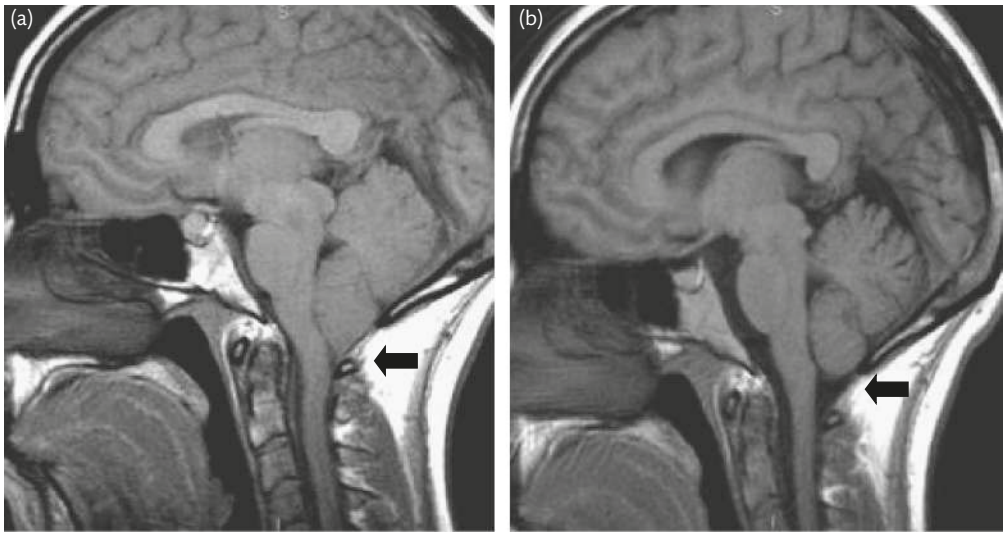

Figure 24.3 (a) Cranial magnetic resonance imaging showing tonsillar descent (arrow) in a patient consulting for cough headache after a lumbar puncture. (b) Resolution of tonsillar descent (arrow) after a lumbar patch.

response to indomethacin the treatment should continue for about 6 months (10,25). Patients with symptomatic cough headache do not consistently respond to any known pharmacological treatment, including indomethacin, and need specific surgical treatment. It has been shown that suboccipital craniectomy with posterior fossa reconstruction relieves cough headache in patients with Chiari type I malformation (10,13).

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25

Exertional and sex headache

Shih-Pin Chen, Julio Pascual, and Shuu-Jiun Wang

Introduction

Exertional headaches (or headaches provoked by prolonged physical exercise) and sexual headaches have been recognized for decades. These two headache disorders share some pathophysiological and clinical characteristics, and might respond to similar pharmacological treatments. They can be either primary (benign) or secondary to intracranial pathology (symptomatic). Investigation of secondary causes is mandatory for patients with these headaches.

Definitions of exertional headache and sexual headache have evolved with time. In 1932, the term 'la céphalée à l'effort' was first coined by Jules Tinel to describe four patients with intermittent paroxysmal headache brought on by exertion or manoeuvres capable of increasing intrathoracic pressure (1). In 1968, E. Douglas Rooke (2) proposed the term 'benign exertional headache' for any headache precipitated by 'exertion', such as running, bending, coughing, sneezing, heavy lifting, or straining at stool. However, 'exertion' defined here actually included a mixture of physical activities with diverse mechanisms, such as Valsalva-like manoeuvres, general physical efforts, or mechanical factors related to the cervical spine. The influence of Rooke remained prior to 1990s such that the term exertional headache actually encompassed cough headache, headache related to prolonged strenuous exercises, and headache attributed to sexual activities. In 1991, Sands et al. (3) analysed a large group of cases with headaches provoked by cough or exertion. In this monograph, benign exertional headache was used to describe severe, short-lived pain after coughing, sneezing, lifting a burden, sexual activity, or other similar brief effort. Structural lesions of the brain or skull, especially posterior fossa mass lesions, were the most common organic aetiologies of these disorders.

Historically, primary sexual headache was also called benign orgasmic cephalgia, benign coital headache, or benign vascular sexual headache, intercourse headache, and so on (4–6). James W. Lance (7) was one of the first among his contemporaries to propose two different subtypes of headaches related to sexual activities. Type 1 was a headache related to muscle contraction that developed as sexual excitement mounted in the pre-orgasmic phase, whereas type 2 was a severe, explosive headache occurring at orgasm, presumably of vascular origin. A third type—post-orgasmic postural headache—had been reported (5), which was recognized as a secondary headache due to low cerebrospinal fluid (CSF) pressure. Lance proposed that headaches related to sexual activities were analogous but distinct from headaches due to cough or exertions (7). However, in an analysis by Silbert et al. (6), 40% of patients with sexual headache also experienced benign exertional headaches. The distinction and relationships of these headaches became clearer when Pascual et al. (8) reported 72 patients with cough, exertional, or sexual headaches in 1996. In this series, 42% of patients were symptomatic and differed from benign ones in several clinical aspects. Benign exertional headaches specifically referred to headaches that occurred during or after strenuous physical exercise, while benign cough headaches were those triggered by cough or Valsalva-like manoeuvres. Similar to the observation of Silbert et al. (6), this study found that 31% of patients with sexual headaches could also fulfil the diagnostic criteria of benign exertional headache proposed by International Headache Society in 1988 (9).

In subsequent prospective epidemiological studies (10–12), benign exertional headaches were used to refer specifically to headaches that occurred during or after sustained strenuous physical exercise, while headaches that were precipitated mainly by Valsalva-like manoeuvres, with sudden mode of onset and short duration, were classified as benign cough headaches. In fact, primary exertional headache (designated as primary exercise headache) and primary cough headache have been clearly defined and separated in the third edition of the International Classification of Headache Disorders (ICHD-3) (see also Chapter 24). Primary headache associated with sexual activities is also coded separately in the ICHD-3, and a considerable association with reversible cerebral vasoconstriction syndrome (RCVS) is mentioned in the comments.

Epidemiology

Hospital-based studies suggested that exertional headache is not a common headache disorder, accounting for 1–2% of the consultations for headache in general neurological clinics (6,8,10) and 5.3% in a headache clinic (13). However, two large-scale epidemiological studies found that the prevalence of exertional headaches is much higher than previously thought (11,12). The prevalence of exertional headache in Norwegian adults is reportedly 12.3%, according to the Vågå study (11), while a report on Taiwanese adolescents found a prevalence of up to 30.4% (12). The discrepancy of prevalence

between hospital-based studies and field research might be due to the fact that most of the exertional headaches are not severe and the sufferers do not usually seek medical help. Possible explanations for the lower prevalence in adults than adolescents might be recall bias of early-life experiences and being less physically active in adulthood. Most of the hospital-based studies found that exertional headaches are more prevalent in males (2,8,10), but these two large-scale field studies, as well as one study performed in a headache clinic, found a female predominance (11–13).

By contrast, the prevalence and sex preponderance of sexual headache is more consistent between clinic-based studies (6,8,10,13–15) and field research (16). The prevalence of headache associated with sexual activities is around 1%. There is a 2–5-fold higher prevalence in males versus females (4,6,8,10,13–15,17). The mean age at onset is around the fourth and fifth decades (4,6,8,10,13–15,17). However, adolescent cases are being increasingly recognized (18,19).

Clinical features

Exertional headache is generally bilateral, pulsating, gradual onset, mild-to-moderate in intensity and short-lasting (8,10,11,20); however, these characteristics are not invariable. For example, the headaches are unilateral in 51% of adolescent patients and pulsating in 59% (12). Most adolescent patients have headaches lasting < 1 hour, but the headache duration tends to be longer in adults (8,10–12,20). Nearly half of patients with exertional headaches have comorbid migraine (6,12,13,20). Migrainous features such as nausea, vomiting, photophobia, or phonophobia are not common in exertional headaches, but patients with comorbid migraine would have exertional headaches with more migrainous features (12,20). The most commonly reported exercises that would lead to headaches include running, various ball games, and swimming. However, some patients might also have headaches that could be elicited by short-lasting Valsalva-like manoeuvres (6,12). This might be owing to the fact that some exercises also involve isotonic or isometric activities simulating Valsalva manoeuvres, and activities that are Valsalva manoeuvres-like can also be strenuous. Another reason might be that Valsalva manoeuvres are actually aggravating factors rather than precipitating factors, but it is difficult for some patients to differentiate between these two.

Sexual headaches are mostly bilateral and predominantly occipital or holocephalic in location (8,10,14,15,21). Most of the sexual headaches are explosive at onset (orgasmic type), but some are of gradual onset with increasing sexual excitement (pre-orgasmic type) (14,15). However, except for the mode of headache onset, these two subtypes do not have significant differences in demographics, clinical features, comorbidities, or prognosis (14). Therefore, in the ICHD-3, these two subtypes are no longer described (22). Sexual headaches are usually severe in intensity, lasting from minutes to hours, with a median duration of 30 minutes (14,15). Nausea, vomiting, and mood disturbance are occasionally noted (14,15). These headaches usually occur during sexual intercourse or orgasm, but also can occur during masturbation and nocturnal emission (8,21,23). Comorbidity with other primary headaches, such as migraine, tension-type headache, or primary exertional headache, is common (6,14,15,21,24).

Diagnosis

Comprehensive investigations for these two headaches are mandatory. Detailed headache history, including the onset of headache (gradual or abrupt) and its temporal relationship with the precipitating factors (what kind of exercise or manoeuvre), headache duration, intensity, location, aggravating and relieving factors, accompanying symptoms (including migrainous features or any newly developed neurological symptoms), blood pressure change, and disease course, are very important. Because secondary headaches might exhibit similar characteristics to these two headache disorders, a careful neurological examination, neuroimaging studies, or other appropriate diagnostic tests (e.g. CSF analysis) are also required.

According to the ICHD-3 criteria, primary exercise headache (code 4.2) was used to replace the term primary exertional headache, and the criteria were revised to cover these possible implicit characteristics of exertional headache in adolescents (**Table 25.1**). Probable primary exercise headache (code 4.2.1) was also proposed in the ICHD-3 for headaches that are believed to be primary exercise headache, but lacking one of the features required to fulfil all the criteria (**Table 25.1**). The ICHD-3 stopped subclassifying primary headache associated with sexual activities by means of a temporal relationship with orgasm (code 4.3; **Table 25.1**). For patients who experience only one attack of '4.3 Primary headache attributed to sexual activity' during their life, or have headaches missing one of the all criteria, probable primary headache attributed to sexual activity can be diagnosed (code 4.3.1; **Table 25.1**).

Of the primary headaches, migraine is the most important one to be differentiated from primary exertional headache. Despite a high comorbidity of exertional headache and migraine, most headaches induced by exercise were phenotypically different from migraine, even in migraineurs. For the minority of exercise-induced headaches that could fulfil the diagnostic criteria of migraine, they should be coded as migraine and not as primary exertional headache.

Differential diagnosis

These two entities are great diagnostic challenges to physicians because the onset of both can be acute and whether the aetiology is primary or secondary cannot be judged based solely on clinical features.

In patients with exertional headaches, secondary causes including subarachnoid haemorrhage, metastatic tumour, sinusitis, arteriovenous malformation, Arnold-Chiari malformation, cardiac cephalalgia, fusiform aneurysms of the vertebral artery, elongated styloid process, and others have been reported (8,10,25–28). Hence, magnetic resonance imaging of the brain or appropriate diagnostic testing is indicated. Magnetic resonance angiography, venography, CSF studies, electrocardiogram, or otorhinolaryngology evaluations are sometimes required when vascular or other disorders are suspected.

The secondary causes of sexual headache include RCVS (see also Chapter 49), subarachnoid haemorrhage (see also Chapter 34), cervical or intracranial arterial dissection (see also Chapters 10 and

Table 25.1 The ICHD-3 diagnostic criteria for primary exercise headache and primary headache associated with sexual activities.

4.2 Primary exercise headache

A. At least two headache episodes fulfilling criteria B and C
B. Brought on by and occurring only during or after strenuous physical exercise
C. Lasting < 48 hours
D. Not better accounted for by another ICHD-3 diagnosis

4.2.1 Probable primary exercise headache

A. Either of the following:
   1. A single headache episode fulfilling criteria B and C
   2. At least two headache episodes fulfilling criterion B but not criterion C
B. Brought on by and occurring only during or after strenuous physical exercise
C. Lasting < 48 hours
D. Not better accounted for by another ICHD-3 diagnosis

4.3 Primary headache associated with sexual activity

A. At least two episodes of pain in the head and/or neck fulfilling criteria B–D
B. Brought on by and occurring only during sexual activity
C. Either or both of the following:
   1. Increasing in intensity with increasing sexual excitement
   2. Abrupt explosive intensity just before or with orgasm
D. Lasting from 1 minute to 24 hours with severe intensity and/or up to 72 hours with mild intensity
E. Not better accounted for by another ICHD-3 diagnosis

4.3.1 Probable primary headache associated with sexual activity

A. Either of the following:
   1. A single headache episode fulfilling criteria B–D
   2. At least two headache episodes fulfilling criterion B and either of criteria C and D
B. Brought on by and occurring only during sexual activity
C. Either or both of the following:
   1. Increasing in intensity with increasing sexual excitement
   2. Abrupt explosive intensity just before or with orgasm
D. Lasting from 1 minute to 24 hours with severe intensity and/or up to 72 hours with mild intensity
E. Not better accounted for by another ICHD-3 diagnosis

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37), rupture of arteriovenous malformation, hypertensive crisis, and hydrocephalus (8,10,15). Considering the high proportion of vascular origin in secondary causes, comprehensive vascular imaging of head and neck is recommended in addition to structural brain imaging studies. When the patient experiences multiple explosive headaches during sexual activities, RCVS should always be considered until proven otherwise. Because vasoconstrictions may not be observed at the early stage of RCVS, follow-up studies may be needed.

Pathophysiology

The pathophysiology of exertional headache remains unclear. It has been proposed that impaired myogenic cerebrovascular autoregulation might play a role, which leads to headaches caused by an aberrant vasodilatation during or following exercise (29). An incompetent internal jugular valve, which leads to transient retrograde venous flow and increased intracranial pressure, was also proposed to be important in the pathogenesis (30). Similarly, stenosis of intracranial venous sinuses has been reported in a few cases (31,32), indicating a potential role of dysfunctional venous system and transient intracranial hypertension. However, this seems to be more plausible in patients with headaches during or after exercises involving components of Valsalva manoeuvres.

Sexual activities are, indeed, a special form of exercise, and thus many aspects of the speculated pathophysiology of sexual headaches are similar to exertional headaches. An impaired metabolic cerebrovascular autoregulation was demonstrated using transcranial Doppler sonography with the acetazolamide test (33). A high percentage of comorbidity between sexual headache and RCVS suggests that an aberrant central sympathetic response and dysfunction regulation of cerebral vascular tone might play an important role (15). In a recent study, it was found that primary headache associated with sexual activity is associated with high percentage (63%) of venous abnormalities, including either transverse sinus or jugular vein stenosis (31). It is mandatory to replicate these findings in another independent cohort to validate the venous hypothesis.

Treatment

There has been no established treatment guideline for exertional headache. Conventional approaches include non-pharmacological and pharmacological interventions. Non-pharmacological interventions focus on preventive aspects, which include bio-behavioural strategies such as proper warm-up before exercise, hydration with a sports drinks, and regular sports training. Pharmacological interventions include preventive, pre-emptive, and acute abortive treatment. If the attacks are infrequent and predictable, pre-emptive treatment can be administered just before exertion. Although anecdotal, indomethacin, taken 1–2 hours before exertion, might be the best choice. For attacks that are frequent or unpredictable, preventive therapy may be the best choice. Beta blockers (nadolol or propranolol) at 1–2 mg/kg daily for 2–6 months might be helpful (8,10). Acute pharmacological treatment may be tailored to clinical characteristics of exertional headache. Acetaminophen or non-steroidal anti-inflammatory drugs (NSAIDs), especially indomethacin, albeit based on only small case studies (34), could be considered in patients with mild-to-moderate attacks. For those whose attacks are more severe, especially if associated with migrainous features, specific antimigraine therapy such as ergotamine or triptans might be effective. In fact, most of the patients with exertional headache do not seek for medical treatment as the attacks are mostly infrequent and mild in intensity (11,12). In contrast, those who attend neurological or headache clinics for exertional headaches are usually disabled, and are the target population to take care with. In cases with very high disability and known venous stenosis, direct retrograde cerebral venography with manometry and even stenting may be considered (32). However, these invasive procedures should only be performed by highly experienced specialists.

The treatment strategies for sexual headaches are quite similar to those for exertional headaches. Because there is highly variable clinical course, treatment should be tailored individually

(14,15). Some patients can lessen the severity or abort the headache by stopping sexual activity when the headaches begin or by taking a more passive role (14,17). Weight loss and an exercise programme might also be helpful. In addition, it is suggested that patients should remain sexually inactive during the acute stage as recurrent attacks are frequent when they resume sexual activities early (14). Daily beta blockers, such as propranolol, metoprolol, and bisoprolol, or a calcium channel blocker, such as verapamil or diltiazem, may be effective for prophylaxis in patients with frequent attacks (6,8,17,35). Indomethacin, 25–100 mg 1–2 hours before intercourse, is effective as a pre-emptive treatment (17). Ergotamine tartrate, methysergide, or naratriptan have also shown positive results (6,8,17,35–37). Because there is substantial overlapping of sexual headache and RCVS, nimodipine, a calcium channel blocker, might also be considered (38). In contrast, vasoconstrictive drugs such as triptans, although possibly effective in aborting the pain, might aggravate vasoconstriction and should not be used until RCVS or dissection has been excluded. Other NSAIDs (ibuprofen and diclofenac), aspirin or paracetamol, given after the onset of headache, are generally ineffective. A recent case report showed that single greater occipital nerve injection with steroid and local anaesthetic effectively aborted sexual headache (39). However, it is difficult to exclude the possibility that the headache remitted spontaneously.

Prognosis

In the Vågå study, it was found that patients with primary exertional headache usually experienced the condition during a circumscribed period in their early life (20). However, 15% of patients could have headaches for more than 30 years. Because this study is not a longitudinal follow-up study, recall bias should be taken into consideration. About 33–50% of patients with sexual headaches could experience relapsing bouts or run a chronic course (≥ 1 year) (15,17). Nevertheless, most of these patients would finally obtain remission at a longer follow-up (4,6,17). Of note, when the sexual headaches are attributed to RCVS, devastating complications, including posterior reversible encephalopathy syndrome, ischaemic stroke, or intracranial haemorrhage, might ensue (40–42). Clinicians should be careful in treating these patients.

Conclusions

Exertional headache and sexual headache have many points in common, such as headache characteristics, high comorbidity with migraine, impaired cerebral autoregulation, or venous stenosis as possible pathophysiology, and good response to beta blocker and indomethacin treatment. They account for a low proportion of headache consultations, but potentially devastating secondary causes such as subarachnoid haemorrhage should be considered. RCVS should be highly suspected in patients with these headache disorders, and their relationship deserves further study. Criteria for these headache disorders have been modified based on recent study findings in the ICHD-3. Current evidence does not mandate us to provide any treatment guideline; randomized, placebo-controlled studies are required.

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26

Hypnic headache

Dagny Holle and David W. Dodick

Introduction

Hypnic headache (HH) is a rare primary headache that occurs only during sleep. It was first described by Neil Raskin in 1988 (1). He reported five men and one woman aged between 65 and 77 years that suffered from strictly nocturnal bilateral headache attacks, which lasted less than an hour. All patients responded favourably to a bedtime dose of lithium, with remission of attacks.

With the gradual introduction of more cases in the published literature, operational diagnostic criteria were established and HH was included in the second edition of the International Classification of Headache Disorders (ICHD-2; subsection primary headaches: code 4.5) (2). HH was defined as a dull headache that typically occurs after the age of 50 years and awakens patients from sleep (**Box 26.1**). Headache attacks should occur more than 15 times a month without cranial autonomic symptoms and with no more than one migrainous feature (i.e. nausea, photophobia, and phonophobia) should accompany the headache. In 2018 new diagnostic criteria of HH were introduced (ICHD-3) (**Box 26.1**; and see Chapter 1). In contrast to the previous diagnostic criteria, headache attacks should occur on more than 10 days a month. The duration of headache attacks was limited up to 4 hours.

Currently, more than 200 cases have been reported in the literature (3–8)ADD. These cases have led to an expanded phenotype. Mild cranial autonomic features, such as lacrimation or rhinorrhoea have been described in a few patients (9,10). The pain is usually mild to moderate, but severe pain has been reported in up to 20% of patients (5). The pain may be unilateral in one-third of cases and attacks usually last from 15 minutes to 180 minutes. While most patients have headache attacks daily or near daily, an episodic subtype (< 15 days per month) may occur.

Epidemiology

As a rare disorder, the prevalence of HH is difficult to determine. The frequency has only been estimated by its occurrence in large tertiary headache centres. At the Headache Clinic at Mayo Clinic in Rochester Minnesota, 1 in 1400 patients suffered from HH (11). In a German headache centre, HH was diagnosed in 0.1% of cases (12). In Spain, 1 in 100 patients with strictly unilateral headache in a tertiary headache centre was found to suffer from HH (13). Population-based estimates are not available. In addition, many patients may remain undiagnosed for years as knowledge of this rare headache disorder is generally not known outside of the specialties of neurology and headache medicine. This hypothesis is supported by the observation that it takes, on average, 5 years for patients to be diagnosed with HH (5). Some case reports show that some patients even suffer from HH attacks for > 20 years until the diagnosis is made (10).

Clinical characteristics

HH is characterized by headache attacks that occur exclusively during sleep, including nocturnal sleep and daytime naps (9,14).

In contrast with the first observation by Raskin (1), more women than men are affected by HH (male-to-female ratio of 1:1.7) (**Table 26.1**) (5). One study compared the clinical features in male and female patients with HH, but it did not discover significant sex-associated differences (15).

On average, HH starts at the age of 60 years, but younger patients and even children have been reported in the literature. Headache attacks usually last 162 ± 74.1 minutes after awakening, which is notably longer than in the initial cases reports. Some patients even describe HH attacks as lasting up to 10 hours (16,17). About two-thirds of patients describe the headache to be of mild or moderate intensity (65%); one-third (35%) reports severe pain. While the initial diagnostic criteria characterized the pain as dull in character, approximately 32% of patients describe other pain characteristics, such as a throbbing, pulsating, sharp, stabbing, or burning perception (5). In addition, HH was initially thought to be invariably bilateral (3), but about one-third of patients with HH have one-sided attacks (32%). The pain location is variable and located in fronto-temporal head region, or the pain may be diffuse and holocranial.

Most patients with HH report a high frequency of headache attacks (20.8 ± 9.9 per month). The majority of these headache attacks occur between 2.00 AM and 4.00 AM (58%). About one-quarter of HH attacks awaken patients between midnight and 2.00 AM (24%), while 17% occur after 4.00 AM. Only a few patients report headache attacks before midnight, and some patients suffer from HH attacks during daytime naps (9,14).

Box 26.1 Diagnostic criteria of hypnic headache according to the ICHD-3 classification

- **A** Recurrent headache attacks fulfilling criteria B–E.
- **B** Developing only during sleep, and causing wakening.
- **C** Occurring on ≥ 10 days/month for > 3 months.
- **D** Lasting from 15 minutes up to 4 hours after waking.
- **E** No cranial autonomic symptoms or restlessness.
- **F** Not better accounted for by another ICHD-3 diagnosis.

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In contrasts to patients with migraine, most patients with HH display some distinct motor activity (e.g. drinking, eating, reading, taking a shower), or at least prefer not to remain supine in bed. However, patients with HH never reach the degree of restlessness or agitation that is characteristically observed in patients with cluster headache. Mild migrainous features are reported by many patients with HH. Nausea is described by about 20% of patients, while 7% describe phonophobia and/or photophobia. Vomiting is not a typical clinical feature of HH and its presence should point to another diagnosis or a symptomatic subtype of HH (Table 26.2).

Until recently, cranial autonomic symptoms or signs were considered rare or absent in patients with HH. However, a number of authors have described patients with HH with mild autonomic features (9,10). Respectively, lacrimation, ptosis, and rhinorrhoea/nasal congestion are experienced by approximately 6%, 2%, and 7% of patients with HH.

Table 26.1 Clinical characteristics in hypnic headache.

Sex(male/female)	37/63 1:1.7
Age at onset (y)	60.4 ± 10.4 (15–78)
Latency to diagnosis (y)	5.0 ± 4.7 (0.2–24)
Duration of attacks (min)	162 ± 74.1 (15–600)
Frequency of attacks/month	20.8 ± 9.9 (5–31)
Intensity of pain • Mild/moderate • Severe	 65 35
Character of pain • Dull • Throbbing/pulsating • Sharp/stabbing/burning	 68 26 6
Side of headache • Bilateral • Unilateral	 68 32
Migrainous features • Nausea • Phono-/photophobia	 21 7
Trigeminoautonomic features • Lacrimation • Ptosis • Rhinorrhoea/nasal congestion	 6 2 7
Motor activity	97

Data are % or mean ± SD (range)

Sleep and polysomnography

Initially, many case reports suggested that HH might be a rapid eye movement (REM) sleep-associated disorder. Some polysomnographic (PSG) studies showed headache attacks arising exclusively from REM sleep (12,18). This observation supported the postulated underlying pathophysiology of hypothalamus dysfunction. Additionally, many patients reported vivid dreams before awakening with a HH attack. However, recent data have not confirmed these early observations. Larger PSG studies showed REM and non-REM (NREM) sleep-associated HH attacks (19,20), interestingly, even in the same patient and during the same night (21). Currently, a total of 58 PSG-monitored HH attacks have been reported in 37 different patients (12,14,18–29). More than half of them occurred from NREM sleep stages (52%), and mainly from sleep stage 2 (38%). The high prevalence of attacks occurring during sleep stage 2 might be explained by the predominance of this sleep stage as a proportion of the total sleep time (21).

Macro- and microstructural analysis of sleep and actigraphy in a patient with HH showed a quantitative reduction in REM sleep (29). After successful treatment with amitriptyline REM sleep increased again. Additionally, cyclic alternating patter that usually reflects disturbing factors, drug manipulations, and subjective sleep quality increased after treatment. The authors concluded that nocturnal hypo-arousal might be involved in the pathophysiology of HH. Similar patterns had already been observed in migraineurs (30–32).

Sleep disordered breathing, particularly obstructive sleep apnoea syndrome (OSAS), was previously thought be associated with HH. Many PSG studies in elderly patient with HH showed an increased apnoea/hypopnea index (AHI) > 5. However, the onset of the recorded HH attacks was not temporally correlated with the observed drop of oxygen saturation (18,20,21). Only one report showed OSAS-triggered HH attacks that were treated effectively with continuous positive airway pressure treatment and nocturnal oxygen supplementation (18). The observed high OSAS rates in HH might be an artefact of the age of the patient population. This hypothesis is supported by data showing that about 80% of healthy persons over the age of 60 years have an AHI > 5 (33).

Headache comorbidities

As certain primary headache disorders are common, more than one-third of patients with HH report a history of migraine (5). It is still unclear if there is a causal or comorbid relationship between these two headache disorders or if their co-occurrence is from chance alone, given the prevalence of migraine and both disorders being more common in women. One patient with HH suffered from primary sexual headache (34). Both headache disorders were successfully treated with indomethacin. One patient was described as having short -lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and HH (35).

Table 26.2 Clinical hints to discriminate between hypnic headache and migraine.

Clinical feature	Hypnic headache	Migraine
Vomiting during headache attacks	–	+
Motor activity during headache attacks	+	–
Onset in elderly patients (< 50 years)	+	–
Triptan response	+/–	+
Lithium response	+	–
Caffeine response	+	+/–
Strict nocturnal headache attacks	+	–

+, typical clinical feature; +/– might occur in some cases, but is not a common observation; -, is usually not observed.

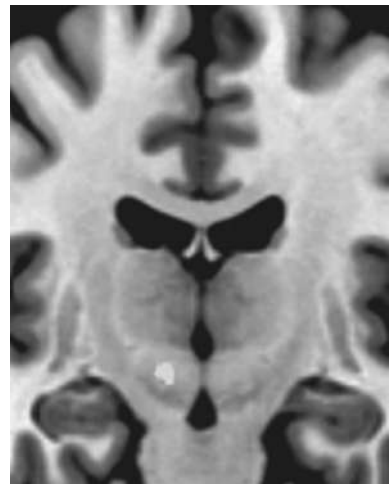

Figure 26.1 (see Colour Plate section) Voxel based morphometry shows decrease in grey matter volume within the posterior hypothalamus. The observed changes support the clinical suspicion of hypothalamic involvement in hypnic headache (46).

Disease course

The course of disease in HH is still unclear. Most studies do not report long-term follow-up of the reported cases. In a Taiwanese study, about half of patients present with an episodic subtype, with an attack period lasting between 7 and 365 days, with sustained remission after treatment (20). Other studies described a relapsing–remitting or even chronic course of disease (20,23,36).

Pathophysiology

The pathophysiology of HH is still enigmatic (37). As distinct circadian rhythmicity with exclusive sleep-related headache attacks is the pathognomonic clinical feature of this disorder, hypothalamic dysfunction was thought to be the source of the attacks. It is well known that descending projections from the hypothalamus terminate in the trigeminal nucleus caudalis and descending orexinergic projections modulate pain at this level. Additionally, the suprachiasmatic nucleus of the hypothalamus is known to play a major role in sleep regulation (38,39). Structural and functional alteration within the hypothalamus has been demonstrated in other primary headache disorders with a circadian rhythmicity such as cluster headache (40–42), in addition to other disorders such as SUNCT (43,44) and paroxysmal hemicrania (45).

A Voxel-based morphometry study showed a significant decrease in grey matter volume within the posterior hypothalamus in patients with HH compared with healthy controls (Figure 26.1) (46). Similar changes have been observed in narcoleptic patients (47). The posterior hypothalamus is known to be strongly connected to the periaqueductal grey, locus coeruleus, and median raphe nuclei, which are involved in descending control of pain perception, as well as in sleep regulation (38,39). Additionally, animal studies suggest that orexins are mainly localized in the posterolateral hypothalamus (48). These neuropeptides are known to be involved in regulation of the sleep–wake cycle by activation of hypocertin type 2 receptors (48). Additionally, the antinociceptive effects of orexins have been described (49). Despite alteration of the hypothalamic grey matter, further structural changes were observed in the so-called general pain network, including the bilateral operculum, frontal lobe, cingulate cortex, and cerebellum (46). These changes seem not to be specific for HH as they were also detected in other chronic pain conditions such as phantom limb pain (50,51), chronic back pain (52,53), fibromyalgia (54,55), neuropathic pain (56), and chronic post-traumatic pain (57).

Only one electrophysiological study has been performed in HH investigating functional changes of trigeminal nociceptive processing using pain-related evoked potentials and nociceptive blink reflex. In contrast to cluster headache and migraine patients, patients with HH did not show any alteration in terms of a facilitation or habituation deficit of evoked trigeminal responses (58).

Paediatric cases

HH in children is a very rare phenomenon and it is still questionable whether these cases should be considered as 'true' HH (59). None of the reported paediatric patients with HH entirely meet the ICHD-2 criteria, mainly owing to low attack frequency (60–62). However, the threshold for the frequency of attacks has been lowered in the revised ICHD-3 criteria. Based on the reported cases, more girls than boys are affected (male-to-female ratio of 1:1.5), which is in line with the adult sex ratio. Mean age was 9 ± 1.6 years. Compared with the adult clinical presentation, HH attack duration was rather short (26.6 ± 11.3 minutes) and attack frequency rather low (9.6 ± 8.6 per month). Two additional adult patients have been reported in the literature who had a onset of their HH attacks during childhood (36,63).

Clinical work-up of HH

A diagnostic algorithm in patients presenting with HH symptoms is displayed in Figure 26.2. In all patients with HH cerebral brain imaging should be performed to rule out symptomatic cases of HH that might present exactly like idiopathic HH. These symptomatic subtypes might include haemangioblastoma of the cerebellum (64), non-functioning pituitary macroadenoma (65), growth hormone-secreting pituitary tumour (66), posterior

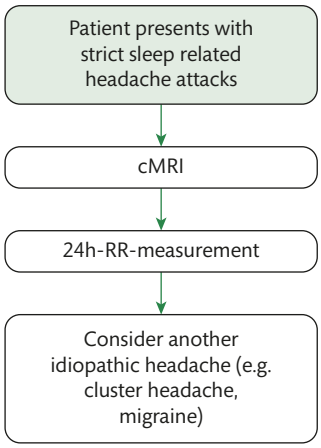
Patient presents with strict sleep related headache attacks
cMRI
24h-RR-measurement
Consider another idiopathic headache (e.g. cluster headache, migraine)

Figure 26.2 Diagnostic algorithm in hypnic headache.
cMRI, cerebral magnetic resonance imaging; RR, blood pressure.

fossa meningioma (67), brain stem lesion (68), and basilar artery dolichoectasia (69).

Besides cerebral lesions, nocturnal arterial hypertension should be ruled out as symptomatic cause of HH. Therefore, 24-hour blood pressure measurement is warranted and should be included in the diagnostic algorithm as it changes the therapeutic approach. In patients with secondary HH caused by nocturnal hypertension, headache might be relieved by antihypertensive medication (70). However, owing to the elderly patient population, up to two-thirds of patients with HH may also suffer from arterial hypertension (20). Most do not report a therapeutic response to antihypertensive medication.

Differential diagnosis

After ruling out underlying causes of the symptoms, the differential diagnosis mainly includes other primary headache disorders, especially migraine and trigeminal autonomic cephalalgias (TACs). Differentiation may be challenging at times, but some clinical features might be helpful. HH is the only headache entity that only occurs during sleep. TACs might present predominantly during nocturnal sleep, but in most cases, attacks also occur during the day in awake patients. Age of onset of HH is usually later than in migraine or the TACs. Most patients with HH show some motor activity, or prefer to be up and out of bed, or at least sitting in bed, while patients with migraine prefer to be supine and still (Table 26.2), which is in strong contrast to the agitation and aggressive motor restlessness that is seen in more than 90% of patients with cluster headache (Table 26.3). Additionally, a therapeutic response to caffeine and general lack of efficacy of triptans can help distinguish HH from migraine.

Therapy

Therapeutic recommendations are only based on case reports, small case series, and clinical experience. Randomized, placebo-controlled trials are not yet available.

Table 26.3 Clinical hints to discriminate between hypnic headache and cluster headache.

Clinical feature	Hypnic headache	Cluster headache
Motor agitation during headache attacks	–	+
Headache attacks longer than 180 minutes	+	–
Excruciating pain intensity	–	+
Pronounced trigeminal autonomic symptoms	–	+
Onset in elderly patients (< 50 years)	+	–
Triptan response	+/–	+
Prednisone response	–	+
Caffeine response	+	–
Oxygen response	–	+
Strict nocturnal headache attacks	+	–

+, typical clinical feature; +/– might occur in some cases, but is not a common observation; –: is usually not observed.

Acute therapy

Caffeine intake in form of a cup of coffee when awakening with headache seems the most effective acute treatment option (Figure 26.2) (9,11,12,17,71–76). Many patients discover this treatment option by themselves before the diagnosis of HH is made. Caffeine-containing analgesics might also be effective in some patients, but the high frequency of HH attacks leads to an excessive consumption of analgesics with the resulting risk of systemic toxicity and medication overuse headache. Most of the other drugs that are commonly used in other primary headache disorders, including triptans (11,12,14,17,36,72,73,77), nonsteroidal anti-inflammatory drugs (9,12,17,36,73,78–80), acetaminophen (9,14,61,77,81), oxygen inhalation (9,13,82,83), metamizole (9), opioids (9), nimesulide (14,17,77,84), and ergotamine (81), have not demonstrated consistent efficacy in patients with HH.

Prophylactic therapy

Prophylactic intake of medication should prevent recurrent nocturnal HH attacks. Adverse side effects, particularly in the elderly given the changes in drug metabolism, elimination, and the risk of polypharmacy and drug interactions, should factor into the decision-making regarding preventive treatment for HH. Only three substances have been shown to be provide reasonably consistent efficacy—lithium carbonate, caffeine, and indomethacin.

Raskin described the effectiveness of lithium in HH treatment in his initial report (1). Since then, lithium has been the most often used preventive drug in HH. Lithium has shown high efficacy rates in up to two-thirds of patients with HH (10,14,17,20,24,27,71,77,78–83,85–90), but bothersome side effects often lead to discontinuation. Additionally, many contraindications have to be considered before starting lithium therapy (e.g. heart and kidney failure, psoriasis, cardiovascular disease, tremor, electrolyte disturbances, hypothyroidism, and concomitant medications with the potential for drug interactions with lithium).

Caffeine appears to be an effective alternative treatment option for some patients, with relatively few side effects (9,11,12,17,71–76). For treatment, a cup of coffee should be consumed before going to bed.

Many patients are afraid of sleep disturbances due to caffeine intake, but this has only rarely been observed. Therefore, patients should be encouraged at least to try this as a first-line treatment option.

Many case reports also report indomethacin as effective for the preventive treatment of HH (9,11,17,23,25,27,34,36,72,74–76,80,89,91–92). Notably, in unilateral headache presentations, indomethacin should be considered as a treatment option (72). However, similar to lithium, indomethacin is associated with the potential for gastrointestinal and renal toxicity, especially in elderly patients, and is therefore often stopped by many patients.

Topiramate (9,77,87), oxoterone (10), and melatonin (9,76,77) have been anecdotally reported to be effective in individual patients Many other drugs have been reported not to be effective in preventing HH attacks or have shown only partial benefit in isolated patients—these include beta blockers (11,14,18,77), verapamil (12,14,17,72), flunarizine (12,14,17,20,77,82,85,95,96), prednisone (11,17,18,71,84,87), benzodiazepines (14,18), gabapentin (17,27,76), antidepressants (18,36,73,75), valproic acid (14,36,77), acetazolamide (93), sodium ferulate (22), and botulinum toxin type A (73). In one patient occipital nerve stimulation was effective (79), and in another one a greater occipital nerve block (97).

Conclusion

HH is a rare primary headache disorder characterized by strictly sleep-related headache attacks. Headaches usually start after the age of 60 years, but onset could be as early as childhood. The underlying pathophysiology is still elusive. Voxel-based morphometry suggests involvement of the hypothalamus in the generation of attacks. Most attacks occur during stage 2 sleep. Cerebral imaging and 24-hour blood pressure measurement should be performed to rule out symptomatic subtypes. Other headache disorders such as cluster headache and migraine may also present with sleep-related headache attacks and should be considered first in nocturnal headache. Therapeutically, caffeine appears to be the first-line acute and prophylactic treatment due to a combination of both efficacy and favourable tolerability; indomethacin and lithium carbonate can also be used for preventive treatment in those resistant to or intolerant to caffeine.

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27

Cranial neuralgias and persistent idiopathic facial pain

Aydin Gozalov, Messoud Ashina, and Joanna M. Zakrzewska

Trigeminal neuralgia

According to the recently published third edition of the International Classification of Headache Disorders (ICHD-3), trigeminal neuralgia (TN) is a recurrent unilateral paroxysmal pain and is divided into 'classical' and "secondary' (1). Classical TN includes all cases with no definitive aetiology identified apart from a vascular compression of the trigeminal nerve. The new classification distinguishing classical TN (with demonstration of morphological changes in the trigeminal nerve root from vascular compression), secondary TN (due to an identifiable underlying neurological disease), and idiopathic TN (unknown aetiology) (1). Those with secondary TN have either a compression of the trigeminal nerve caused by tumours (benign and malignant) or other structural abnormalities such as arteriovenous malformations, or have multiple sclerosis (MS). In ICHD-3, TN is divided into a 'purely paroxysmal' form and a form 'with concomitant persistent facial pain' (1). Those patients who do not fulfil all the diagnostic criteria identified by the International Headache Society **Box 27.1** (2) have variously been termed atypical TN type II TN and, according to ICHD-3 criteria, classical TN with concomitant persistent facial pain (1,3–5). However, TN should be differentiated from other facial pain disorders (**Table 27.1**).

Epidemiology

Katusic et al. (6) estimated the incidence rate of TN at 4.3 per 100,000. TN occurs more frequently in women than in men (female-to-male ratio of 3:2).Incidence rates increase with age and are highest in those aged 60 years and older (6,7). However, recent primary care surveys from both the UK (8) and the Netherlands (9) show much higher incidences of 26.8 and 28.9 per 100,000, respectively, but it was shown that misdiagnosis was common (10). A European study using a sample of 602 patients with neuropathic pain found that 14% had TN (11). The UK survey (8) showed a higher incidence in women of all age groups, and a peak incidence between 45 and 59 years of age, which is lower than reported previously. However, it is likely that some of the cases were potentially misdiagnosed as dental pain, sinusitis, or even temporomandibular disorders, as these can present with symptoms similar to TN, especially when episodic and unilateral (12).

Pathophysiology

TN is a unique form of neuropathic pain and the true cause of TN is still unknown. It is believed that both peripheral and central dysfunction play an important role. It has been suggested that vascular compression of the TN root entry zone causes focal demyelination and secondary ephaptic transmission. The prevailing hypothesis of the aetiology of TN is outlined by Devor et al. (13) as the 'ignition hypothesis'. The hypothesis states that the trigger stimuli set off bursts of activity in the small cluster of trigeminal ganglion neurons that have been rendered hyperexcitable as a result of ganglion or trigeminal root damage (13). Activity then spreads from this ganglion ignition focus to encompass more widespread portions of the ganglion. These partially injured sensory neurons thus become hyperexcitable and exhibit a phenomenon known as 'after discharge'. These afterdischarge bursts may be triggered by an external stimulus and extend beyond the duration of the stimulus. They can then also recruit additional neighbouring neurons, leading to a rapid build-up of electrical activity, which results in a paroxysmal explosion of pain. After a brief period of autonomous firing, the activity is quenched by an intrinsic suppressive (hyperpolarizing) process, making the nerve refractory to further excitation (13). In addition, Obermann et al. (14) reported central facilitation of trigeminal nociceptive processing in patients with TN with concomitant chronic facial pain, suggesting overactivation of central sensory transmission.

Clinical features

The patient history is essential to diagnose TN and therefore all patients must be carefully interviewed by a physician. Pain is described as brief, paroxysmal, lasting from a split second to 2 minutes, and described as superficial, intense, lancinating, stabbing, shooting, or like electric shocks or lightning. Pain can be evoked or spontaneous. Pain distribution is unilateral and follows the sensory distribution of the trigeminal divisions, typically radiating to the maxillary (V2) or mandibular (V3) territories. Ophthalmic (V1) on its own is less

Box 27.1 Classification Committee of the International Headache Society: The International Classification of Headache Disorders

13.1.1 Classical trigeminal neuralgia

Previously used term: tic douloureux.

Description: trigeminal neuralgia developing without apparent cause other than neurovascular compression.

Diagnostic criteria

A At least three attacks of unilateral facial pain fulfilling criteria B and C.

B Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution.

C Pain has at least three of the following four characteristics:

1 Recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes

2 Severe intensity

3 Electric shock-like, shooting, stabbing or sharp in quality

4 Precipitated by innocuous stimuli to the affected side of the face.

D No clinically evident neurological deficit.

E Not better accounted for by another ICHD-3 diagnosis.

13.1.1.1 Classical trigeminal neuralgia, purely paroxysmal

Description: trigeminal neuralgia without persistent background facial pain.

Diagnostic criteria

A Recurrent attacks of unilateral facial pain fulfilling criteria for 13.1.1 Classical trigeminal neuralgia.

B No persistent facial pain between attacks.

C Not better accounted for by another ICHD-3 diagnosis.

Comment: 13.1.1.1 Classical trigeminal neuralgia, purely paroxysmal is usually responsive, at least initially, to pharmacotherapy (especially carbamazepine or oxcarbazepine).

13.1.1.2 Classical trigeminal neuralgia with concomitant persistent facial pain

Previously used terms: atypical trigeminal neuralgia; trigeminal neuralgia type 2.

Description: trigeminal neuralgia with persistent background facial pain.

Diagnostic criteria

A Recurrent attacks of unilateral facial pain fulfilling criteria for 13.1.1 Classical trigeminal neuralgia.

B Persistent facial pain of moderate intensity in the affected area.

C Not better accounted for by another ICHD-3 diagnosis.

Comments: 13.1.1.2 Classical trigeminal neuralgia with concomitant persistent facial pain has been referred to as atypical trigeminal neuralgia, or, recently, as trigeminal neuralgia type 2. Central sensitization may account for the persistent facial pain. Neurovascular compression on MRI is less likely to be demonstrated. Classical trigeminal neuralgia with concomitant persistent facial pain responds poorly to conservative treatment and to neurosurgical interventions. It is less likely to be triggered by innocuous stimuli.

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common and is considered indicative of symptomatic TN. The pain can be experienced extra-orally, intra-orally, or both. It is not felt in the teeth, but around them. The right side of the face is involved more frequently than the left. There is no pain between paroxysms and after an attack of pain there is a refractory period when the nerve cannot be stimulated. There is often an after-pain, described as burning or dull, which slowly fades away. Paroxysms may occur several times a day. Especially in the early years of the condition there can be long periods of no pain, but these remission periods gradually become shorter and shorter. The pain severity varies, but with time becomes worse and leads to reduced quality of life and depression.

Pain may be provoked by stimulating cutaneous or mucosal trigeminal territories (trigger zones), regardless of the distribution of the perceived pain. Gently touching the face, washing or shaving, talking, brushing the teeth, chewing, swallowing, or even a slight breeze can trigger the paroxysms. Up to a third of patients will report the pain to affect their sleep. Adjunctive signs may occur during paroxysms. Pain provokes brief muscle spasms of the facial muscles, thus producing the tic. Lacrimation, rhinorrhoea, or redness of the face is very rare, but is noted, and it can then be difficult to distinguish from short unilateral neuralgiform headache with autonomic features (SUNA) and these could be the same disorder (see also Chapter 20) (15).

ICHD-3 diagnostic criteria for 13.1.1 Trigeminal neuralgia

Description

A disorder characterized by recurrent unilateral brief electric shock-like pains, abrupt in onset and termination, limited to the distribution of one or more divisions of the trigeminal nerve and triggered by innocuous stimuli. It may develop without apparent cause or be a result of another diagnosed disorder. Additionally, there may be concomitant continuous pain of moderate intensity within the distribution(s) of the affected nerve division(s).

Previously used terms

Tic douloureux, primary trigeminal neuralgia.

Diagnostic criteria

Recurrent paroxysms of unilateral facial pain in the distribution(s) of one or more divisions of the trigeminal nerve, with no radiation beyond,[1] and fulfilling criteria B and C.

A. Pain has all of the following characteristics:

1. Lasting from a fraction of a second to 2 minutes[2]
2. Severe intensity[3]
3. Electric shock-like, shooting, stabbing or sharp in quality.

B. Precipitated by innocuous stimuli within the affected trigeminal distribution.[4]

C. Not better accounted for by another ICHD-3 diagnosis.

Notes

1. In a few patients, pain may radiate to another division, but it remains within the trigeminal dermatomes.

2. Duration can change over time, with paroxysms becoming more prolonged. A minority of patients will report attacks predominantly lasting for > 2 minutes.

3. Pain may become more severe over time.

4. Some attacks may be, or appear to be, spontaneous, but there must be a history or finding of pain provoked by innocuous stimuli to meet this criterion. Ideally, the examining clinician should attempt to confirm the history by replicating the triggering phenomenon. However, this may not always be possible because of the patient's refusal, awkward anatomical location of the trigger, and/or other factors.

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Table 27.1 Diagnostic criteria of trigeminal neuralgia (TN) and how these compare with other differential diagnoses

Symptom	TN	Pulpitis	TMD	Neuropathic trigeminal pain	SUNA/SUNCT	Paroxysmal hemicrania
Character	Shooting, stabbing, electric	Sharp, aching, throbbing	Dull, aching, nagging	Aching, throbbing	Burning, stabbing, sharp	Throbbing, boring, stabbing
Site/radiation	Trigeminal distribution, intra/extra-oral	Around a tooth, intra-oral	Pre-auricular, radiates down mandible, temple area	Around tooth or area of past trauma/dental surgery	Peri-orbital but can affect maxillary division	Orbit, temple
Severity	Moderate to severe	Mild to moderate	Mild to severe	Moderate	Severe	Severe
Duration	1–60 s refractory period	Rapid but no refractory period	Not refractory, lasts for hours, mainly continuous can be episodic	Continuous soon after injury	Episodic 5–240 s	Episodic 2–30 min
Periodicity	Rapid onset and termination, complete periods of remission weeks to months	Unlikely to be > 6 months	Tends to build up slowly and diminish slowly, lasts for years	Continuous	Numerous, can be periods of complete remission	1–40 a day, can be periods of complete remission
Provoking factors	Light touch, non-nociceptive	Hot/cold applied to teeth	Clenching teeth, prolonged chewing, yawning	Light touch	Light touch	Nil
Relieving factors	Keeping still, drugs	Avoid eating on that side	Rest, decrease month opening	Avoid touch	Nil	Indomethacin
Associated factors	Local anaesthetics placed in trigger area relives pain, severe depression and weight loss	Decayed tooth, exposed dentine	Muscle pain in other parts of the body, limited opening, clicking on wide opening	History of dental treatment or trauma in the area, may be loss of sensation, allodynia near pain, local anaesthetic relieves pain	Often restless, ipsilateral cranial autonomic symptoms	May have migrainous features, ipsilateral cranial autonomic symptoms

SUNA, short-lasting unilateral neuralgiform headache attacks with with cranial autonomic features; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; TMD, temporomandibular disorder.

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Comments

The diagnosis of '13.1.1 Trigeminal neuralgia' must be established clinically. Investigations are designed to identify a likely cause. Other than the triggering phenomenon, most patients with '13.1.1 Trigeminal neuralgia' fail to show sensory abnormalities within the trigeminal distribution unless advanced methods are employed (e.g. quantitative sensory testing). However, in some, clinical neurological examination may show sensory deficits, which should prompt neuroimaging investigations to explore possible cause.

Diagnosis of subforms, such as '13.1.1.1 Classical trigeminal neuralgia', '13.1.1.2 Secondary trigeminal neuralgia', or '13.1.1.3 Idiopathic trigeminal neuralgia', is then possible.

When very severe, the pain often evokes contraction of the muscles of the face on the affected side (tic douloureux).

Mild autonomic symptoms such as lacrimation and/or redness of the ipsilateral eye may be present.

Following a painful paroxysm there is usually a refractory period during which pain cannot be triggered (reproduced from (1)).

About 15% of cases are secondary to major neurological disease such as tumours or MS (symptomatic TN) (16). A recent systematic review of pain in patients with MS shows a prevalence of 3.8% (95 confidence interval 2–6) and reviews of the literature on the characteristic of MS-related TN show that there is considerable overlap in symptoms between classical TN and that occurring in MS (17). De Santi and Annunziata conclude that there are no reliable clinical predictors to differentiate these (18). Many patients with symptomatic TN have symptoms of typical TN (although both tumours and MS may also induce other types of facial pain without the characteristics of typical TN). In other words, the pain is indistinguishable from ICHD-3 diagnostic criteria for classical TN but caused by a demonstrable structural lesion other than vascular compression. There may be sensory impairment in the distribution of the appropriate trigeminal division.

Traditionally, the clinical features that were considered indicators of probable symptomatic TN were:

- bilateral pain;
- sensory deficits;
- involvement of the ophthalmic division;
- unresponsiveness to medical treatment;
- onset age < 50 years;
- ipsilateral ear symptoms, such as hearing loss or a feeling of fullness, can indicate the presence of schwannomas or acoustic neuromas;
- the finding of bedside sensory deficits may be an indicator of symptomatic TN, but their absence does not indicate classical TN.

However, sensory abnormalities in TN have been debated (13,19) and reported (14,20) in previous studies. A prospective systematic study of clinical characteristics in 158 patients documented sensory abnormalities in TN (21), and the authors proposed modified

ICHD-3 criteria with shown improved sensitivity (22). The involvement of the ophthalmic division is uncommon in TN. The absence of response to antiepileptic drugs, however, should also lead to very careful reconsideration of the diagnosis. The mean age at onset was significantly lower in symptomatic (48 years) compared with in classical (57 years) TN, but the histogram of onset age distribution showed that there was considerable overlap in the age ranges of the two populations (23). Thus, although younger age increases the risk of finding symptomatic TN, the diagnostic accuracy of age as a predictor of symptomatic TN is too low to be clinically useful.

However, there are other patients that have many of the features of classical TN but who also have more prolonged pain. This has variously been called TN type 2 (5), TN with concomitant pain (14), and now classical TN with concomitant persistent facial pain (ICHD-3).

Investigations

As it is impossible to exclude a symptomatic form on clinical grounds alone, performing neuroimaging at least once in all patients is recommended (23,24). Recent advances in neuroimaging have proved the ability to diagnose symptomatic TN. Neuroimaging will identify the cause in patients with symptomatic TN—that is, MS plaques or compressive mass. The magnetic resonance imaging (MRI) protocol for TN assessment is used to both identify these cases and determine whether there is a vascular compression of trigeminal nerve. Recent guidelines from the American Academy of Neurology (AAN) and the European Federation of Neurological Societies (EFNS) have failed to find sufficient evidence to support or refute the fact that the presence of a neurocompression is the cause of TN (23,24). It is also noted that neurovascular contact can be seen in 15–20% of people with no TN, but the authors did not grade the neurovascular contact (24). A recent study demonstrated that neurovascular contact was prevalent both on the symptomatic (89%) and asymptomatic side (78%), while severe neurovascular contact (causing displacement or atrophy of trigeminal nerve) was highly prevalent on the symptomatic (53%) compared with the asymptomatic side (13%) (25,26). This study concluded that severe neurovascular contact caused by arteries located in the root entry zone was involved in the aetiology of classical TN (26).

Medical management

There are now several systematic reviews, including Cochrane reviews, detailing the evidence base and use of drugs in TN, in addition to guidelines for both general practitioners and specialists (23,24,27,28–34). Unfortunately, there have been few high-quality randomized controlled trials (RCTs), and many were conducted using small cohorts in single centres. The major drugs are summarized in Table 27.2.

All drugs will result in neurological side effects such as drowsiness, ataxia, and diplopia at higher doses.

Carbamazepine (CBZ) is the drug of choice, as shown in Table 27.2. It is highly effective and, in newly diagnosed patients, is likely to provide complete pain relief within a few days. It needs to be started at a low dose and increased slowly in order to minimize side effects. However, this drug causes multiple adverse effects, including drug interactions (35). Therefore, this has led to the search for other similarly effective drugs with potentially less problematic side effect

Table 27.2 Major drugs used in the medical management of trigeminal neuralgia

Drug	Daily dose range	Side effects	Use	Comments
Drugs used in RCTs				
Carbamazepine (CBZ)	200–1000 mg	Drowsiness, ataxia, nausea, headaches, blurred vision	Begin with small doses, extended release version useful at night	Beware drug interactions (e.g. warfarin–CBZ, so dosages may need to be adjusted)
Oxcarbazepine	300–1200 mg	Better tolerated than CBZ, drowsiness, ataxia, hyponatremia at higher doses	Use on four-times-a-day basis	Hyponatraemia at higher doses
Baclofen	50–80 mg	Ataxia, lethargy, fatigue, nausea, loss of muscle tone	Begin very slowly, frequent dosage	Withdraw drug slowly to avoid side effects. Useful in patients with MS
Lamotrigine	200–400 mg	Dizziness, drowsiness, ataxia, diplopia, rapid dose escalation leads to rashes	Initially very slow escalation. Good when added to another AED	Rashes common if dose increased too quickly
Gabapentin with ropivacaine	1800–3600 mg gabapentin (RCT utilized up to 900 mg) with 4 mg ropivacaine injected into each trigger point	Sedation, ataxia, dizziness, oedema	Ropivacaine injected weekly into trigger areas	Use of ropivacaine reduced dose of gabapentin required
Drugs not evaluated in RCTs				
Phenytoin	200–300 mg	Gum hyperplasia, depression, diplopia, ataxia	Can use with CBZ	> 300 mg can lead to severe side effects
Sodium valproate	600–1200 mg	Nausea, gastric irritation, diarrhoea, weight gain, hair loss	Often used by neurologists	May take weeks to see a response
Pregabalin	150–600 mg	Abnormal gait, balance or coordination problems, blurred vision, concentration problems	Effective used twice daily	Long-term cohort study shows promise

RCT, randomized controlled trial; MS, multiple sclerosis; AED, antiepileptic drug.

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profiles. Recent guidelines have suggested that the second-line drug should be oxcarbazepine (OXC), which is, in fact, a prodrug of CBZ (23,24). This drug does not use the liver cytochrome system and therefore does not result in such widespread drug interactions and is generally better tolerated. It must, however, be remembered that, given the chemical similarity of these drugs, allergic cross-reactions between the two drugs can occur. According to recent guidelines (23,33), patients who reach effective doses of CBZ or OXC but who do not experience enough pain relief become candidates for surgical interventions. There is now evidence to suggest that females are more sensitive to both CBZ and OXC and lower dosages should be used in females (35). Patients who cannot reach effective doses of CBZ and OXC because of contraindications or adverse events should try second-line drugs (36). Although there are cases series reporting the efficacy of several new drugs, there has only been one RCT, which demonstrated efficacy of lamotrigine as an add-on therapy (37). More recently, a RCT of gabapentin with regular ropivacaine injections into the trigger sites suggested that this combination was highly effective. However, the patients in this trial were newly diagnosed and may therefore have been likely to go into remission (34). The AAN/EFNS guidelines suggest that lamotrigine and baclofen are other second-line drugs that could be prescribed (23,24). There is a RCT of Botox (38), which suggests that it can be effective, but there are several methodological shortcomings (39). Linde et al. (40) suggest that Botox is not effective. Pregabalin has been shown to be effective in a long-term, well-conducted cohort study (41).

Oral phenytoin (historically, the first antiepileptic drug used for the treatment of TN) is effective in only 25% of patients and its chronic administration has potentially serious adverse effects (24). However, phenytoin can be administrated intravenously and thus it is useful in emergency, when extremely frequent TN paroxysms preclude taking anything orally (42).

A new selective sodium channel blocker is currently being investigated and is showing promising results (43).

There are no placebo-controlled studies regarding the medical management of symptomatic TN. The existing studies all deal with TN associated with MS and are small, open-label trials. Lamotrigine, gabapentin, topiramate, misoprostol (a prostaglandin E1 analogue) and baclofen have been reported to be efficacious in patients with TN and MS (22,32,44). Figure 27.1 provides an algorithm for the treatment of TN.

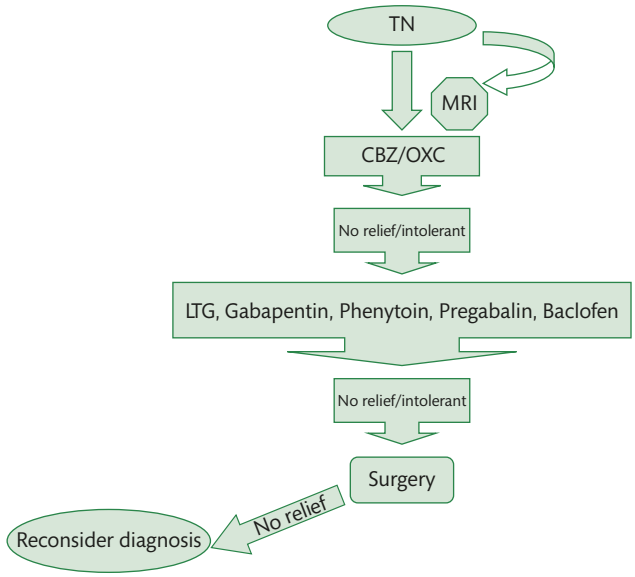

Figure 27.1 Algorithm for the treatment of trigeminal neuralgia (TN). MRI, magnetic resonance imaging; CBZ, carbamazepine; OXC, oxcarbazepine; LTG, lamotrigine.

Surgical therapy

There is now increasing evidence to suggest that early surgical treatment may be appropriate, especially in patients with classical signs of TN and in whom MRI investigations show evidence of neurovascular compression of the trigeminal nerve. Candidates for surgical treatment for TN include patients who have failed medical therapy or patients who initially responded but later became intolerant to medical therapy and whose quality of life has markedly diminished. There is a Cochrane review of surgical interventions with only three higher-quality studies (45) and no RCTs involving microvascular decompression.

There is a wide variety of surgical treatments available and only one of these, microvascular decompression, aims to preserve trigeminal nerve function. All of the other procedures can be termed destructive or ablative, as they aim to reduce sensory input and hence give rise to a degree of nerve damage. The interventions are performed at three target areas:

- peripheral—that is, distal to the Gasserian ganglion at specified trigger points;
- Gasserian ganglion level;
- posterior fossa at the root entry zone;
- the data are based on the AAN/EFNS findings (23,24).

Peripheral techniques

A wide variety of peripheral techniques have been described, including cryotherapy, neurectomies, peripheral acupuncture, peripheral radiofrequency thermocoagulations (RFTs), and a variety of injections, such as alcohol, phenol. and streptomycin. Only the latter has been reported in two RCTs, which demonstrated that it was ineffective (46,47). Recent case study suggests that peripheral nerve field stimulation can be an effective treatment for refractory facial pain inclusive TN (four patients) (48).

There is still insufficient evidence to support the use of peripheral treatments unless patients are medically unfit and request an instant procedure. Pain relief is in the order of 10 months.

Percutaneous procedures at the level of the Gasserian ganglion

All percutaneous procedures involve the insertion of a cannula through the foramen ovale into the trigeminal ganglion under heavy sedation of short general anaesthetic. The ganglion can then be lesioned using heat (RFT), injection of glycerol, or mechanical compression by the use of a balloon. Usually, an overnight inpatient stay is required for these procedures. There is limited evidence to support these treatments, with only two RCTs both comparing different techniques for RFT, with pain intensity being the primary outcome measure (49–51). There is minimal evidence from prospective case series that have used independent outcome measures (52). The major outcome measure has been pain

relief, and there are only a handful of studies that have measured quality of life. Up to 90% of patients are likely to obtain immediate pain relief, but this gradually reduces so that, by 5 years, about 50% of patients will have a recurrence of pain. Mortality is understandably low with regard to these procedures. Given that all these interventions are destructive, varying degrees of sensory loss are reported. This sensory loss can be very mild; however, up to 4% of patients may report severe anaesthesia dolorosa. When the treatments involve the first division of the trigeminal nerve, then eye problems such as corneal numbness and keratitis are possible. Pulsed peripheral RFT is a procedure whereby the RFT applied at the level of the Gasserian ganglion is a pulsed rather than a continuous current. The perceived benefit of pulsed over continuous is the reduction in postoperative sensory loss. However, current evidence suggests the pain relief outcome of pulsed RFT is inferior compared with traditional RFT (49).

Gamma knife surgery

This is an ablative procedure, which targets the trigeminal root entry zone on the posterior fossa and aims to focus a beam of radiation at this point. There have been trials to determine both the optimum dose of radiation and its precise location (51). Initial reports suggested that this procedure was the most acceptable, as it was the least invasive and resulted in no side effects. However, as data have now been accumulating, there is evidence to show that sensory loss also occurs in these patients, albeit often with delay for some months after the procedure. In those studies using independent outcome measures, it would appear that pain relief periods are similar to those procedures that are performed at the Gasserian ganglion level. Data using a non-validated questionnaire suggest the quality of life is improved. Complete pain relief was achieved in 65.5% (13.8% with low-dose and 51.7% without medication). Pain improved partially in 17.2% of participants and another 17.2% had no benefit. The median time for complete pain relief was 3 months after radiosurgery (range 1 week–17 months) and relapse occurred in 34.5%. Numbness or paraesthesia reported in 24% of patients. No severe adverse effects were reported. Assessments took place at 6 months, 12 months, and then at yearly intervals (51).

There are an increasing number of case series being reported but no systematic review, and the general consensus appears to be that pain relief can take up to 3 months to occur and that the long-term results are similar to other ablative procedures, with 50% being pain free at 5 years. Sensory loss can be delayed beyond the time of pain relief and varying sensory abnormalities can occur, including anaesthesia dolorosa (53).

Microvascular decompression

Microvascular decompression is the only non-destructive procedure, but it is the most invasive operation of all those done for TN.

A craniotomy is performed in the postauricular area, which enables the trigeminal nerve to be exposed and vessels to be identified and then moved out of direct contact with the trigeminal nerve. There are no RCTs and only a handful of studies that have used independent outcome measures (54). Given that this is a major neurosurgical procedure, it follows that it will be associated with mortality, which varies from 0.2% to 0.5%. This is considerably lower than when the procedure was first reported some 27 years ago. It has been shown in the USA that high-volume units are likely to have lower mortalities and lower postoperative morbidity (55). Most of the complications tend to be in the early postoperative period and include cerebrospinal fluid leaks, haematomas, aseptic meningitis, diplopia, and facial weakness. The major long-term complication is ipsilateral hearing loss, which can be as high as 10%.

Overall, when reporting practice guidelines, the AAN/EFNS could only state that the longest duration of pain relief could be obtained in patients undergoing microvascular decompression, 70% are pain free at 10 years, and that there is a lack of direct comparative studies between the different surgical techniques (23,24). However, quality of life is likely to be better after a microvascular decompression given there is no longer any need for medications and the fear of pain return has gone. Moreover, the degree of neurovascular contact could be important when selecting patients for surgery (26).

A recent prospective systematic study showed that neurovascular contact with morphological changes and male sex are positive predictive factors for outcome of microvascular decompression. The findings enable clinicians to better inform patients before surgery (56).

Recent reviews of patients seen in neurology units suggest that only a small percentage go on to have surgery (n = 13/178; 7%) (57).

Patients need to make several decisions about treatment and this is difficult given the lack of evidence but marginally patients think surgical interventions are the better option (58). To help them further patients can be directed to patient support groups, which are a good source of information (59).

Glossopharyngeal neuralgia

Glossopharyngeal neuralgia is a severe transient stabbing pain experienced in the ear, base of the tongue, tonsillar fossa, or beneath the angle of the jaw. The pain is therefore felt in the distributions of the auricular and pharyngeal branches of the glossopharyngeal nerve. It is commonly provoked by swallowing, talking, or coughing and may remit and relapse in the fashion of TN. Stimulation of the vagus can result in syncope. In most cases, this condition is idiopathic, but some instances might be due to symptomatic causes, again compression of the nerve by tumours or malformations. Patients will suffer from episodes of pain lasting for weeks or months, and then have periods of remission. The attacks themselves also last for no more than 2 minutes. Again, the pain is unilateral.

ICHD-3 diagnostic criteria for 13.2.1 Classical glossopharyngeal neuralgia

Previously used term

Vagoglossopharyngeal neuralgia.

Description

A disorder characterized by unilateral brief stabbing pain, abrupt in onset and termination, in the distributions not only of the glossopharyngeal nerve, but also of the auricular and pharyngeal branches of the vagus nerve. Pain is experienced in the ear, base of the tongue, tonsillar fossa, and/or beneath the angle of the jaw. It is commonly provoked by swallowing, talking, or coughing, and may remit and relapse in the fashion of trigeminal neuralgia.

Diagnostic criteria

A. Recurring paroxysmal attacks of unilateral pain in the distribution of the glossopharyngeal nerve[1] and fulfilling criterion B.

B. Pain has all of the following characteristics:
1. Lasting from a few seconds to 2 minutes
2. Severe intensity
3. Electric shock-like, shooting, stabbing, or sharp in quality
4. Precipitated by swallowing, coughing, talking, or yawning.

C. Not better accounted for by another ICHD-3 diagnosis.

Note

1. Within the posterior part of the tongue, tonsillar fossa, pharynx or angle of the lower jaw, and/or in the ear.

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Comments

'13.2.1 Glossopharyngeal neuralgia' can occur together with '13.1.1 Trigeminal neuralgia'. Reproduced from (1).

Epidemiology

Glossopharyngeal neuralgia is rare, with an incidence rate of 0.7 per 100,000, and it has been reported to co-exist with TN (60). It occurs in older age groups and seems to predominate in women. There are no data on prognosis but, judging by the few reports of surgical treatment, it would appear that patients have a less severe history than those with TN. There are no RCTs reporting the use of any drugs in glossopharyngeal neuralgia. The largest review of patients with TN, by Rushton et al. (61) in 1981, suggested the same drugs as for TN and half of the patients eventually underwent surgical management (61). Other drugs have been reported mainly as single-case reports: pregabalin, lamotrigine, OXC, CBZ, gabapentin (62–66).

ICHD-3 diagnostic criteria for 13.12 Persistent idiopathic facial pain

Previously used term

Atypical facial pain.

Description

Persistent facial and/or oral pain, with varying presentations but recurring daily for more than 2 hours/day over more than 3 months, in the absence of clinical neurological deficit.

Diagnostic criteria

A. Facial and/or oral pain fulfilling criteria B and C.

B. Recurring daily for > 2 hours/day for > 3 months.

C. Pain has both of the following characteristics:
1. Poorly localized, and not following the distribution of a peripheral nerve
2. Dull, aching or nagging quality.

D. Clinical neurological examination is normal.

E. A dental cause has been excluded by appropriate investigations.

F. Not better accounted for by another ICHD-3 diagnosis.

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Comments

A wide variety of words are used by patients to describe the character of '13.12 Persistent idiopathic facial pain', but it is most often depicted as dull, nagging, or aching, either deep or superficial. It can have sharp exacerbations, and is aggravated by stress. With time, it may spread to a wider area of the craniocervical region.

Patients with '13.12 Persistent idiopathic facial pain' are predominantly female.

'13.12 Persistent idiopathic facial pain' may be comorbid with other pain conditions such as chronic widespread pain and irritable bowel syndrome. In addition, it presents with high levels of psychiatric comorbidity and psychosocial disability.

Persistent idiopathic facial pain (PIFP), previously termed 'atypical facial pain', is a persistent facial pain that does not have the characteristics of cranial neuralgias and cannot be attributed to a certain disorder. The facial pain occurs daily and persists throughout the day. Generally, it is limited to one particular area on one side of the face at disease onset, is deep and poorly localized, and is not associated with sensory loss or other neurological deficits (67). Investigations, including X-ray of the face and jaws or cranial computed tomography or MRI, do not demonstrate any relevant abnormality. The exact cause and pathophysiology of this syndrome is not known, and the syndrome may be a collection of different conditions. These patients are often found to also have diffuse musculoskeletal conditions such as fibromyalgia, myofascial pain syndrome, and chronic fatigue syndrome (68). Antidepressant medications and cognitive behavioural therapy may play a beneficial role in treating PIFP (69).

ICHD-3 diagnostic criteria for 13.1.2.3 Painful post-traumatic trigeminal neuropathy

Previously used term

Anaesthesia dolorosa.

Coded elsewhere

Here are described painful post-traumatic neuropathies; most trigeminal nerve injuries do not result in pain and therefore have no place in ICHD-3.

Description

Unilateral facial or oral pain following trauma to the trigeminal nerve, with other symptoms and/or clinical signs of trigeminal nerve dysfunction.

Diagnostic criteria

A. Unilateral facial and/or oral pain fulfilling criterion C.

B. History of an identifiable traumatic event to the trigeminal nerve, with clinically evident positive (hyperalgesia, allodynia)

and/or negative (hypoaesthesia, hypoalgesia) signs of trigeminal nerve dysfunction.

C. Evidence of causation demonstrated by both of the following:
1. Pain is located in the distribution of the same trigeminal nerve
2. Pain has developed within 3–6 months of the traumatic event.

D. Not better accounted for by another ICHD-3 diagnosis.

Note

The traumatic event may be mechanical, chemical, thermal, or caused by radiation. Reproduced from (1).

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Comment

Pain duration ranges widely from paroxysmal to constant, and may be mixed. Specifically following radiation-induced postganglionic injury, neuropathy may appear after more than 3 months.

It is now increasingly recognized that trauma to the trigeminal nerve can result not just in neuropathy, but also in long-term neuropathic pain. Many patients previously diagnosed as having 'atypical facial pain' are probably patients that, in fact, belong to this group. The pain may be initiated by surgery or injury to the face, teeth, or gums, but it persists without any demonstrable local cause.

The use of specific local analgesics (articaine in 4% solutions for mandibular blocks) is suspected to cause permanent nerve lesions resulting in persistent pain and sensory disturbance within the affected facial area (70,71). In addition, molar extractions in the lower jaw may also cause a permanent painful lesion within the mandibular division of the trigeminal nerve. There is also the highly specific condition 'atypical odontalgia', which is defined as pain in a tooth, or a tooth-bearing area, which is not related to any dental cause and again is often mistaken as toothache and treated with multiple dental treatments (66,72,73). The pain is continuous in a tooth socket, even after tooth extraction. These pains may, in fact, constitute a subset of trigeminal neuropathic pain and have been well characterized by Baad-Hansen (74) and List et al. (72). It has been suggested that it should be termed persistent dento-alveolar pain disorder (75), and studies show central changes (76).

Neurophysiological testing shows that these patients have peripheral and central sensitization changes, but there is also some evidence for nociceptive changes, which might therefore be important in the choice of drugs (77). Currently, there are no data on the epidemiology of neuropathic pain, but it has been suggested that a risk factor for this could be inadequate anaesthesia during dental procedures, as this increases the risk for potential central sensitization. As with anywhere else in the body, trauma and compression of sensory nerves can result in long-term neuropathic pain.

The increasing recognition of this condition puts increasing challenges on clinicians to manage this pain. A topical approach is the use of lidocaine or capsaicin patches, or even clonazepam. It may provide some benefit, especially if the pain is provoked by light touch activities and interferes with sleep. Some patients have found that the advantage of having a good night's sleep enables them to cope better with their neuropathic pain throughout the day. However, as trials have shown, it is highly likely that trigeminal neuropathic pain also results in central changes and therefore there is a requirement for systemic drugs. Nortriptyline, often in lower doses than recommended in guidelines, seems to result in a 30% pain reduction. Pregabalin appears to be especially useful in patients who also show a high level of anxiety. Topical lidocaine may again be useful in those patients whose sleep is interrupted due to the allodynia.

The clinical features of trigeminal neuropathic pain are shown in Figure 27.2.

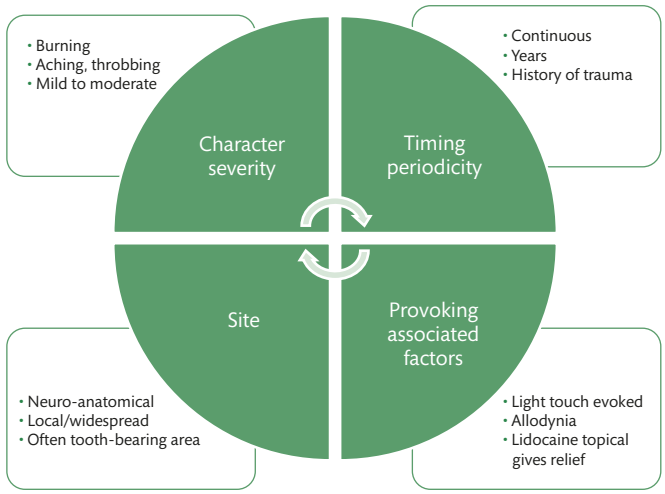

Figure 27.2 Clinical features of trigeminal neuropathic pain.
Reproduced from *Orofacial Pain* (ed) Joanna M. Zakrzewska. Copyright (2009) with permission from Oxford University Press.

ICHD-3 diagnostic criteria for 13.11 Burning mouth syndrome

Previously used terms

Stomatodynia, or glossodynia when confined to the tongue.

Description

An intra-oral burning or dysaesthetic sensation, recurring daily for more than 2 hours daily over more than 3 months, without clinically evident causative lesions.

Diagnostic criteria

A. Oral pain[1] fulfilling criteria B and C.

B. Recurring daily for > 2 hours daily for >3 months.

C. Pain has both of the following characteristics:
1. Burning quality[2]
2. Felt superficially in the oral mucosa.

D. Oral mucosa is of normal appearance and clinical examination, including sensory testing, is normal.

E. Not better accounted for by another ICHD-3 diagnosis.

Notes

1. The pain is usually bilateral; the most common site is the tip of the tongue.

2. Pain intensity fluctuates.

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Comments

Subjective dryness of the mouth, dysaesthesia, and altered taste may be present.

There is a high menopausal female prevalence, and some studies show comorbid psychosocial and psychiatric disorders. Laboratory investigations and brain imaging have indicated changes in central and peripheral nervous systems. Reproduced from (1).

Comment

Burning is usually bilateral and its intensity fluctuates. The most common site is the tip of the tongue. Subjective dryness of the mouth, dysaesthesia, and altered taste may be present. There is a high menopausal female prevalence, and some studies show comorbid psychosocial and psychiatric disorders. Recent laboratory and brain imaging investigations have indicated changes in central and peripheral nervous systems showing that this is probably a neuropathic pain (78).

Secondary burning mouth can be due to local (candidiasis, lichen planus, hyposalivation) or systemic causes (medication induced, anaemia, deficiencies of vitamin B12, folic acid, Sjögren syndrome, diabetes), or drugs.

Associated factors

As with all pain conditions facial pain patients often experience high levels of psychological distress and physical disability (79). A study by Taiminen (80) of 63 patients with burning mouth syndrome or atypical facial pain showed that over 50% of these patients had a lifetime mental health disorder. Depression and personality disorders were common, and these often were present prior to the facial pain. These comorbidities may have a significant effect on treatment outcomes and so a multidisciplinary approach to treatment is essential. Patient treatment goals must also be taken into consideration, as McCracken et al. (81) have shown that treatment satisfaction among chronic pain patients receiving standard pain clinic interventions (pharmacological treatment, nerve blocks, epidural steroid injections, etc.) was only weakly related to the degree of pain relief they obtained. The strongest predictors of treatment satisfaction were a belief they had been given a full and complete assessment, and the provision of an explanation for the treatments that were being delivered. A recent review of treatments for burning mouth syndrome suggest that cognitive behaviour therapy is likely to be beneficial and there is insufficient evidence to support the use of alpha lipoic acid, benzydamine, clonazepam, or any antidepressants (82).

Conclusion

Although some of the neuralgias are unique to the face, patients with these conditions will all have psychological responses that are similar to other patients with chronic pain and so are best managed by multidisciplinary teams. For some of the conditions there are now some guidelines based on RCTs, but for many of them there remains a lack of high-quality studies and treatments are based on case series reports or extrapolated from other conditions with similar mechanisms.

Update

Readers should refer to the updated 2019 guidelines for the latest information [83].

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28

Some rare headache disorders, including Alice in Wonderland syndrome, blip syndrome, cardiac cephalalgia, epicrania fugax, exploding head syndrome, Harlequin syndrome, lacrimal neuralgia, neck–tongue syndrome, and red ear syndrome

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Introduction

Alice in Wonderland syndrome, blip syndrome, cardiac cephalalgia, epicrania fugax, exploding head syndrome, Harlequin syndrome, lacrimal headache, neck–tongue syndrome, and red ear syndrome are among the fascinating array of rare headache disorders. James W. Lance, Juan A. Pareja, and colleagues have first described or named six of them. Certainly, there are patients with additional rare headaches just waiting to be described by astute observers.

In case of a rare headache disorder, an appropriate diagnosis and treatment can be most reassuring to the patient.

Alice in Wonderland syndrome

History

In 1952, Caro W. Lippman described seven migraineurs who had unusual distortions of body image (1). The descriptions are illustrative: 'Occasionally the patient has an attack where she feels small, about 1 foot high.' Another patient had the sensation of 'her left ear ballooning out six inches or more'. A third patient described his sensations: 'the body is as if someone had drawn a vertical line separating the two halves. The right half seems to be twice the size of the left half.' And a fourth noted, 'I feel that my body is growing larger and larger until it seems to occupy the whole room.' One of the patients who felt short and wide while she walked referred to her abnormal sensation as her Tweedledum or Tweedledee feeling (two characters from Lewis Carroll's 1871 book, *Through the Looking-Glass, and What Alice Found There* (2)). Lippman concluded, '*Alice in Wonderland* [full title, *Alice's Adventures in Wonderland* (3)] contains a record of these and many other similar hallucinations. Lewis Carroll (Charles Lutwidge Dodgson), who wrote "Alice," was himself a sufferer from classic migraine headaches.'

In 1955, Todd, in giving the syndrome its name, presented six new cases and described a syndrome of distortions of the size, mass, or shape of the patient's own body or its position in space often associated with depersonalization and derealization (4). Distortions in the perceived passage of time were also described in some patients. Todd discussed the many causes in addition to migraine. Since then, many authors have used Alice in Wonderland syndrome (AIWS) for the visual illusions and distortions of how others appear rather than illusions of one's own body as in Todd's original description.

Alice's Adventures in Wonderland was published in England in 1864 by Dodgson under the pseudonym of Lewis Carroll (the Latinization of Lutwidge Charles). Dodgson was a Professor of Mathematics at Oxford University and a migraineur. There is speculation that he might have had the syndrome (5–7).

In the first chapter of the book, Alice jumps down a rabbit hole and lands in a hallway where she finds a bottle, which she drinks from, causing her to shrink: ' "I must be shutting up like a telescope." And so it was indeed: she was now only 10 in high.' Later, she eats a piece of cake that makes her grow (**Figure 28.1**): ' "Curiouser and couriouser!" cried Alice.; "now I'm opening out like the largest telescope that ever was! Good-bye, feet!" (for when she looked down at

Figure 28.1. Alice stretched tall.
Illustration by Sir John Tenniel, 1865.

her feet, they seemed to be almost out of sight, they were getting so far off.)'

Clinical features and aetiology

AIWS syndrome is a rare migraine aura usually where patients experience distortion in body image characterized by enlargement, diminution, or distortion of part of or the whole body, which they know is not real (8–10). The syndrome can occur at any age but is more common in children. A 1-year prospective observational study of young people aged 8–18 years found that AIWS can occur before the onset of headaches, may go unrecognized, and may be more common than previously realized (11). The symptoms are attributed to the non-dominant posterior parietal lobule.

In a review of 81 cases, the cases were categorized as somaesthetic (n = 7; 9%), visual (n = 61; 75%), or both (n = 13; 16%) (12). Epstein–Barr virus infection was commonly identified (n = 39; 48%) followed by migraine (n = 11; 14%). Other possible associations included other infectious disorders (varicella, H1N1 influenza, coxsackievirusB1, scarlet fever, typhoid fever, and, not included in the review, an association with Lyme neuroborreliosis (13)), acute Zika virus infection (14), and mycoplasma infection (15), toxic encephalopathy, major depression, epileptic seizures, medications (cough syrup with dihydrocodeine phosphate and DL-methylephedrine hydrochloride (16), topiramate, and aripiprazole (17)), a right medial temporal lobe stroke, and a right temporo-parietal cavernoma (18). Six of the migraine cases were somaesthetic and two had somaesthetic and visual symptoms.

In a series of 20 paediatric cases, the average age was 9.5 ± 3.8 years (range 4–16 years) (19). Ninety per cent had micropsias and/or macropsias, 85% distortion of the form of the objects, 80% displacement of objects, 45% disturbances of body image, 45% acceleration of time, and 30% a sensation of unreality. Ninety-five per cent of the children had many episodes a day; these episodes lasted less than 3 minutes in 90% of them. Neuroimaging was normal in all cases. Migraine was considered the cause in eight and Epstein–Barr virus infection in five. The majority of cases had spontaneous resolution without recurrence. Another paediatric series of nine children followed-up for a mean of 4.6 years also showed only occasional recurrence, in two (20). There is a case report of a 15-year-old female with AIWS following acute Zika virus infection (14).

There is a single case report of a 17-year-old male with a history of abdominal migraine since the age of 10 years who developed AIWS (21). All of his symptoms improved after treatment with valproate.

Topiramate has been reported as causing AIWS 1 week after starting 25 mg daily (titrating up to 100 mg daily over 4 weeks) in a 31-year-old woman with chronic migraine (22,23). She described episodes of her entire body feeling either too big or too small and everything else either too small or too big (or two episodes of feeling too big and then too small) all lasting 5–10 minutes, followed by a mild headache behind the eyes lasting 30–45 minutes without medication. The symptoms resolved 1 month after stopping topiramate.

A 17-year-old female with episodic migraine developed distortions of body image where her head would grow bigger and the rest of her body would shrink or her hand would increase in size and become heavier while the rest of the arm would become smaller only when she did not directly fall asleep after taking topiramate 75 mg at bedtime (24). The symptoms resolved on 50 mg at bedtime and reappeared on 75 mg at bedtime, and then ceased when she stopped the drug except for one episode 3 months later. An electroencephalogram and magnetic resonance imaging (MRI) of the brain were normal.

Routine neuroimaging studies in migraineurs with the syndrome are normal. Not surprisingly, there are no placebo-controlled studies on treatment of what appears to be a rare and self-limited migraine variant.

Prognosis

Of the 15 patients with follow-up with AIWS seen by a paediatric neuro-ophthalmologist over 20 years, 20% had a few more events, which eventually stopped after the initial diagnosis, 40% had no more events, and 40% were still having symptoms at follow-up (25). Twenty-seven per cent developed migraines and 7% developed seizures following the diagnosis of AIWS.

In a follow-up study over 30 years of 28 patients with paediatric migraine precursors, more than one-quarter still experienced distortions of time and nearly 20% still reported distortions of space (26).

Blip syndrome

History

Lance had unusual sensations himself for about 6 months, which he recognized were not associated with his cardiac extrasystoles, which he named 'blip' syndrome (27). He then reported 12 additional cases (including eight women; three physicians) ranging in age from 33 to

75 years with symptoms present for periods of 2 months up to 5 years, with a typical frequency of episodes of 1–4 per month (five had two or more per day and one had 12–15 per day on some occasions) with each lasting a split second up to 2 seconds (28). Interestingly, four of 12 were migraineurs and none had seizure disorders.

Clinical features

Patients described sensations including 'a short circuit in the brain', their mind 'going blank for a second' with a pressure in the forehead and a 'feeling of losing balance', 'impending loss of consciousness', and 'a wave going through'. Testing on some of the patients, including electroencephalograms (EEGs), computed tom scans, electrocardiograms, and carotid ultrasounds were normal.

Case report

In 2013, I evaluated a 47-year-old man with a history of 'little small short circuits', which had been occurring for 7 months and which usually occurred 2–3 times per day up to 10 times per hour. He described a blip in his head that he did not see or feel but sensed for a half a second. The symptom could occur when sitting, standing, or walking but not when lying down. He had no alteration of consciousness, vertigo, paraesthesias, weakness, trouble speaking, associated headache, or other neurological symptom except for a brief feeling of slight imbalance.

There was a history of episodic migraine without aura since childhood and hyperlipidaemia. Neurological examination was normal.

He had seen another neurologist. MRI of the brain with and without contrast and magnetic resonance angiography of the brain were negative. Evaluation by an ear-nose-and-throat physician, including audiogram and electronystagmography, were normal. EEG was normal. Cardiac evaluation was normal.

Aetiology

The aetiology of the episodes is not certain. Lance compared blip syndrome to other benign disorders such as déjà vu, night starts, and exploding head syndrome (see 'Exploding head syndrome').

Cardiac cephalalgia

Clinical features

Cardiac ischaemia may rarely cause a unilateral or bilateral headache brought on by exercise and relieved by rest. This is called 'cardiac cephalalgia', or 'anginal headache' (29–31). Headaches may occur alone or be accompanied by chest pain. In cases of unstable angina, headaches may also occur at rest (32). Even a thunderclap headache may accompany the chest pain (33).

Thirty-six well-documented cases of cardiac cephalalgia were reported in the literature up to 2013: 58.3% were males, usually over the age of 50 years (but 22% were younger than 50—the youngest 35) (34). Anti-anginal medications (nitrates) caused headaches in 56% of cases (35). Thirty per cent had associated symptoms such as photophobia, phonophobia, osmophobia, and nausea (36). Chest pain, pain in the left arm, sometimes radiating to the mandible or epigastric region, was present in 50% of cases. Cardiac cephalalgia was the only manifestation of angina in 27% of cases. Five more cases have been subsequently reported (37).

Cardiac cephalalgia should be distinguished from migraine as the use of triptans or dihydroergotamine, in general, is contraindicated in cardiac ischaemia and might even be harmful. Appropriate cardiac testing will make the diagnosis once suspected. The headaches resolve with revascularization or conservative treatment.

Migrainous thoracalgia, a diagnosis of exclusion, is a migraine accompanied by an aura of chest pain and arm paraesthesias which can occur with or with headache (38).

Pathophysiology

Angina is generally believed to be the result of afferent impulses that traverse cervicothoracic sympathetic ganglia, enter the spinal cord via the first and the fifth thoracic dorsal roots, and produce the characteristic pain in the chest or inner aspects of the arms. Cardiac vagal afferents, which mediate anginal pain in a minority of patients, join the tractus solitarius.

Although the cause is not known, a potential pathway for referral of cardiac pain to the head would be convergence with craniovascular afferents (39). Two other possible mechanisms of headache have been suggested (25): (i) a reduction of cardiac output and an increase in right atrial pressure during myocardial ischaemia can be associated with reduction in venous return, which increases intracranial pressure producing headache; and (ii) release of chemical mediators resulting from myocardial ischaemia (serotonin, bradykinin, histamine, and substance P) may stimulate nociceptive intracranial receptors and produce headache.

Epicrania fugax

History

Pareja et al. (40) described 10 patients with a novel syndrome in 2008, which they named 'epicrania fugax', with over 100 cases reported (41–43). Eight cases are associated with nummular headache (44).

Clinical features

Epicrania fugax is characterized by paroxysmal pain through the surface of one side of the head in a linear or zig-zag trajectory, which may move forward or backward and is not in the distribution of one single nerve. So the pain may go between the posterior scalp and the ipsilateral forehead, eye, and nose. The pain, which typically has an electrical quality, is of moderate or severe intensity and lasts one to a few seconds. The frequency ranges from a few attacks per year or less to numerous attacks per day. There may be associated ipsilateral cranial autonomic symptoms such as conjunctival injection, lacrimation, or rhinorrhoea. The pain may shift sides. Between attacks, some patients have a persistent mild pain or tenderness in the area where the pain originates.

Neurological examination was normal in all patients except for local hypersensitivity at the area where the pain originates in a few patients. Diagnostic testing, including neuroimaging and erythrocyte sedimentation rates, was normal.

Five patients have been reported with similar pain starting in the lower face (V2 or V3) and radiating upwards with a linear trajectory of moderate-to-severe intensity with a stabbing or electrical quality lasting one to a few seconds (45).

Management

Gabapentin and lamotrigine have been reported as providing partial or complete relief for some patients. A few patients have benefited from pregabalin, levetiracetam, and carbamazepine. Amitriptyline, indomethacin, occipital nerve blocks, and trochlear injections have also been occasionally effective (33,34,46).

Exploding head syndrome

History

Exploding head syndrome (EHS) was first named by John M.S. Pearce in 1988 when he reported on 10 patients (47). Robert Armstrong-Jones provided the first description as 'snapping of the brain' in 1920 (48), although Silas Weir Mitchell may have previously described the disorder in 1890 (49).

Clinical features

EHS is characterized by a momentary loud noise that patients usually experience during the early stages of sleep (50). Patients describe a sudden onset of 'an explosion in the head', enormous roar, bomb-like explosion, or lightning crack that awakens them from sleep. This is usually followed by a feeling of intense fear, terror and/or palpitations. However, there is no headache or pain associated with the noise.

Symptoms can arise from any stage of sleep, but primarily during stages 1 and 2 (51). One study of nine patients indicated that symptoms correlated with an alert state or awakening on polysomnographic recordings (52). Attacks can occasionally occur as patients are awakening following arousal and onset back to stage 1 sleep. The frequency is highly variable with a range of 2–4 attacks followed by prolonged or lifetime remission to seven attacks nightly for several nightly each week.

Fear, terror, palpitations, or a forceful heartbeat were reported as occurring after the loud noise in 47/50 patients (38). Ten per cent of patients described an associated flash of light and 6% reported a curious sensation as if they had stopped breathing and had to make a deliberate effort to breathe again—'an uncomfortable gasp' (38). Occasionally, brief myoclonic jerks of the extremities or the entire body may follow (53). Psychological stress and being tired may be triggers (38,41). Three patients of 50 reported a positive family history (38).

EHS may be a migraine aura. Kallweit et al. (54) reported a 54-year-old man with attacks of EHS followed by an exacerbation of his chronic migraine after each attack. Evans (55) reported a 26-year-old woman with a history of migraine without aura with multiple episodes of EHS followed by brief sleep paralysis and then one of her typical migraine headaches. The exact cause of EHS, however, is unknown (56). Rossi et al. (57) reported a middle-aged man with EHS as an aura symptoms of migraine with brainstem aura.

Epidemiology

EHS can occur at any age, but is more common in patients older than 50 years of age, with a median age of 54 years (range 12–84 years) and a female-to-male ratio of 3:2 (58,59). The prevalence is unknown as, anecdotally, patients may not report their symptoms. No large-scale prevalence studies have been performed and EHS has been believed to be rare. However, in a study of 211 US college students, 18% had a lifetime prevalence and 16.6% had recurrent cases, not more common in females (60).

Evaluation

The diagnosis is made by the clinical history. A sleep study does not assist in diagnosis and it is not certain whether the study changes management if the patient is found to have obstructive sleep apnoea (see 'Management') (51). The neurological exam is normal. Imaging studies are not necessary, although some patients may wish to be reassured that they do not have a tumour or aneurysm.

Management

After explanation and reassurance, most patients do not require medication. For those with frequent or disturbing symptoms, there are anecdotal reports of benefit of treatment with clomipramine (41), nifedipine (61), flunarizine (45), topiramate (62), amitriptyline (58), and the use of an oral appliance for a patient with obstructive sleep apnoea (48).

Harlequin syndrome

History

Harlequin syndrome was first described by Lance and colleagues in 1988 (63). The syndrome is named after Arleccino (Harlequin) who was a character in the travelling improvisational theatre, which originated in Venice in the sixteenth century, Comedia Dell'Arte (64). Members wore Harlequin masks with blackening of one side (Figure 28.2), which was a similar appearance of the sweating half of the face that was demonstrated with application of alizarin powder (Figure 28.3).

Clinical features

Harlequin syndrome presents with unilateral erythema or redness and hyperhidrosis of the face and, less commonly, the ipsilateral arm and upper chest (65), and is believed to be due to a normal or exaggerated response to the contralateral interruption of the sympathetic nerve fibres, resulting in a vasomotor deficit of the ipsilateral side and often an exaggerated vasodilatory response on the contralateral side during thermal (exposure to heat or exercise) or emotional stimulation. There is one case report where the leg was also involved (66).

Aetiology

Abnormalities should be excluded at the level of the first or several thoracic roots such as mediastinal and pulmonary masses (67). Harlequin syndrome has also been reported as a sequelae of internal jugular catheterization, peri-operative local anaesthesia, sympathectomy to treat severe hyperhidrosis (68), toxic goitre (69), spontaneous cervical carotid artery dissection (70), and implantation of intrathecal pumps (71), obstetric epidural anaesthesia (72), upper lobectomy (73), excision of a neck schwannoma (74), and a neuroblastoma (75). In most cases, no cause is found.

Management

Usually no treatment is required and patients are reassured by an explanation of a cause. A contralateral thoracic sympathectomy could

Figure 28.2 Harlequin mask.

Reproduced from *Practical Neurology*, 5, Lance JW, Harlequin syndrome, pp. 176–177. Copyright (2005) BMJ Publishing Group Ltd.

Figure 28.3 Harlequin syndrome.

Sweating on the right half of the face delineated by the application of alizarin powder.

Reproduced from *Journal of Neurology, Neurosurgery & Psychiatry*, 51, Lance JW, Drummond PD, Gandevia SC, Morris JG, Harlequin syndrome: the sudden onset of unilateral flushing and sweating, pp. 635–642. Copyright (1988) by permission of BMJ Publishing Group Ltd. DOI: 10.1136/pgmj.2009.080473.

be performed to restore symmetry if desired by the patient (54), although most patients do not choose any treatment.

Lacrimal neuralgia

Anatomy

The ophthalmic division of the trigeminal nerve divides into the frontal nerve (which divides into the supratrochlear and supraorbital nerves), the nasociliary nerve, and the lacrimal nerve. The lacrimal nerve runs along the upper border of the lateral rectus muscle in the orbit and splits into two branches, the lateral branch (which supplies the lacrimal gland) and the medial branch (sensory innervation to the lateral aspect of the upper eyelid and adjacent area of the temple) (Figure 28.4).

History

Pareja and Cuadrado reported the first two cases of lacrimal neuralgia in 2013 (76).

Patient 1

A 66-year-old woman had a history of constant moderate-to-severe sore and burning pain, which was worse with lateral eye movements, in the lateral aspect of her left superior eyelid and adjacent area of the temple with onset at age 64 years, without prior trauma or other relevant disease. Neurological examination showed decreased sensation in the area supplied by the left lacrimal nerve and tenderness on palpation between the globe and the external edge of the left orbit. Ophthalmological examination was normal.

MRI of the brain and orbits and blood tests, including thyroid tests, an erythrocyte sedimentation rate, and immunological screening, were normal. Her emotional state was not affected on testing. A left lacrimal nerve block with 2% lidocaine produced complete improvement for around 4 hours. She had absolute relief with pregabalin 150 mg daily. After 9 months, pregabalin was stopped.

Figure 28.4 Skin area supplied by the left lacrimal nerve (shaded area).

The lacrimal nerve gives sensory innervation to the lateral upper eyelid and a small cutaneous area adjacent to the external canthus.

Reproduced from *Cephalalgia*, 33, Pareja JA, Cuadrado ML. Lacrimal neuralgia: So far, a missing cranial neuralgia, pp. 1998–1202. Copyright © 2013 by permission of SAGE. DOI: 10.1177/0333102413488000,

The same symptoms recurred after 4 months, and she had the same absolute relief when pregabalin was resumed.

Patient 2

A 33-year-old woman had a history of constant moderate-to-severe pressure or stabbing pain in a small area adjacent to the lateral canthus of her left eye since the age of 25 years, with an unremarkable medical history. The symptomatic area was tender to light touch. Combing her hair on the left side or chewing could occasionally trigger paroxysmal exacerbations.

Neurological examination showed superficial hypoaesthesia, hyperaesthesia, and allodynia in the left lacrimal nerve distribution. The supero-external angle of the left orbit was hypersensitive to palpation. Ophthalmological and psychiatric evaluations were normal.

A MRI of the brain and orbits was normal. Blood tests, including thyroid tests, an erythrocyte sedimentation rate, and immunological screening, were normal. A lumbar puncture was normal. Four lacrimal nerve blocks with 2% lidocaine resulted in complete relief lasting up to 6 hours. Oral indomethacin, ibuprofen, gabapentin, flunarizine, carbamazepine, oxcarbazepine, topiramate, amitriptyline, duloxetine, mirtazapine and tramadol did not help. Lidocaine patches and capsaicin cream in the symptomatic area were of no benefit. Pulsed radiofrequency of the lacrimal nerve, the Gasserian ganglion, the sphenopalatine ganglion and the ophthalmic nerve did not help. Pregabalin 400 mg daily provided partial but substantial relief.

Three additional cases with negative testing have responded to lacrimal nerve blocks (77).

A secondary case of lacrimal neuralgia has been reported in a woman who developed similar pain attacks lasting 1–2 minutes after left cataract surgery, which was relieved by an anaesthetic block at the emergence of the lacrimal nerve (78), and another in a 53-year-old man with attacks triggered by argon laser photodynamic therapy and intravitreal injection of aflibercept relieved by lacrimal blocks (79).

Summary

Lacrimal neuralgia is a newly reported cause of orbital and periorbital pain which, so far, seems to only be partially or completely responsive to pregabalin or lacrimal nerve blocks. The features and response to treatment of future cases will be of interest.

Neck–tongue syndrome

History

James Cyriax reported two cases of neck–tongue syndrome in 1962 (80). Lance and Anthony named the syndrome when they reported four additional cases in 1980 (81). This is a rare disorder with a prevalence in the Vågå study of 0.2% (82) and over 50 cases reported in the literature (80,83–85).

Clinical features

Neck–tongue syndrome is characterized by acute, unilateral occipital pain lasting a few seconds to 1 minute and numbness of the ipsilateral tongue lasting seconds to 5 minutes precipitated by sudden movement, usually rotation, of the neck to either side. Less frequently, dysarthria, dysphagia, tongue paralysis, or tongue movements may occur (86–90). Intermittent and then constant tongue paraesthesias have been reported (82). Rarely, symptoms may switch sides (78).

Pathophysiology

The symptoms are the result of transient subluxation of the atlantoaxial joint that stretches the joint capsule and the C2 ventral ramus, which contains proprioceptive fibres from the tongue originating from the lingual nerve to the hypoglossal nerve to the C2 root (Figure 28.5) (76,91,92). Contraction of the accessory atlantoaxial ligament (Arnold's ligament) during rotation might irritate the second cervical nerve root, as well as the hypoglossal nerve at its exit from the foramen magnum in some cases (93).

Aetiology

Neck–tongue syndrome can be idiopathic without obvious abnormalities. A benign, familial form of neck–tongue syndrome is described without anatomical abnormality, which resolves spontaneously during adolescence. About 25% of cases have pathology of the occipito-atlantoaxial joints. Secondary causes of neck–tongue syndrome include head and neck trauma, Chiari 1 malformation, congenital anomalies of the cervical spine, ankylosing spondylitis, degenerative spondylosis, rheumatoid arthritis, tuberculous atlantoaxial osteoarthritis, and cervical acute transverse myelopathy

Figure 28.5 Lateral view of the right atlantoaxial joint; the atlas has rotated to the right.

The small arrow shows the inferior articular process impinging the C2 spinal nerve and ventral ramus.

Reproduced from *Headache*, 40, Evans RW, Lance JW, Transient headache with numbness of half the tongue, pp. 692–693. Copyright (2000) with permission from John Wiley and Sons.

(94–97). A prolonged slouching sitting posture has been proposed as a cause (98).

Management

The most effective treatment is not known (29). Non-steroidal anti-inflammatory drugs, muscle relaxants, medications for neuropathic pain (amitriptyline, gabapentin, and carbamazepine), and steroids have been reported to be helpful in single cases. Other treatments reported include cervical collars, analgesics, manipulation, injections of local anaesthetic, nerve resection, and cervical fusion.

Red ear syndrome

History and clinical features

Since Lance first described red ear syndrome in 1994 (99), more than 80 cases have been reported in children and adults (100–103). The disorder is characterized by episodic burning pain, usually in one ear lobe, associated with flushing or reddening of the ear with a duration of seconds to hours (constant in two cases). The average age for idiopathic cases is 35 years with 62% females and for secondary cases 50 years with 70% females.

In individuals, one ear, alternating ears, or occasionally both ears simultaneously can be involved in attacks that can occur rarely or up to 20 times daily. The redness can occur without pain. The pain may radiate to the cheek, forehead, a strip behind or below the mandible, behind the ear, occiput, and the ipsilateral upper posterior neck. Attacks may be spontaneous or precipitated (in 31% of idiopathic cases and 63% of secondary cases) by touching the ear, drinking, coughing, chewing, sneezing, neck movement, exercise, stress, or exposure to heat or cold.

Anatomy

To understand secondary causes, it is helpful to recall the sensory supply of the ear, which includes C2 and C3, and cranial nerves V, VII, IX, and X. The anterosuperior ear lobe is supplied by the auriculotemporal nerve (from V3) and the inferoposterior ear lobe is supplied by the greater auricular nerve (C2 and C3). The blood supply to the ear comes from an anastomosis between branches of the middle temporal and posterior auricular arteries, part of the external carotid circulation innervated by the trigeminal nerve.

Aetiology

RES can be idiopathic or occur in association with migraine (during or between headache episodes), trigeminal autonomic cephalgias, thalamic syndrome, atypical glossopharyngeal and trigeminal neuralgia, upper cervical spine pathology (cervical arachnoiditis, cervical spondylosis, traction injury, Chiari malformation, or herpes zoster of the upper cervical roots), and dysfunction of the temporomandibular joint.

Pathophysiology

Lance postulates that the cause might be an antidromic discharge of nerve impulses in the third cervical root and greater auricular nerve in response to some local pain-producing lesion in the upper neck or trigeminal areas of innervation. Al-Din et al. (104) suggest that primary and secondary cases may be due to activation of the trigeminal-autonomic reflex.

Management

A variety of treatments have been tried with variable success, including gabapentin, amitriptyline, indomethacin, flunarizine, nimodipine, ibuprofen, and indomethacin (105). Local anaesthetic block or section of the third cervical root might be helpful. Some cases are resistant to treatment.

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PART 5

Tension-type and other chronic headache types

29. **Tension-type headache: classification, clinical features, and management** *259*
Stefan Evers

30. **New daily persistent headache** *267*
Kuan-Po Peng, Matthew S. Robbins, and Shuu-Jiun Wang

31. **Chronic migraine and medication overuse headache** *275*
David W. Dodick and Stephen D. Silberstein

32. **Frequent headaches with and without acute medication overuse: management and international differences** *284*
Christina Sun-Edelstein and Alan M. Rapoport

33. **Nummular headache** *298*
Juan A. Pareja and Carrie E. Robertson

29

Tension-type headache

Classification, clinical features, and management

Stefan Evers

Introduction

Tension-type headache (TTH) is divided according to the headache classification of the International Headache Society (IHS) into three subtypes: infrequent episodic TTH (< 1 headache day per month), frequent episodic TTH (1–14 headache days per month), and chronic TTH (≥ 15 headache days per month) (**Box 29.1**) (1,2). This division may seem artificial but is highly relevant for several reasons (3,4). Firstly, impact on quality of life differs considerably between the three subtypes. Secondly, the pathophysiological mechanisms also differ significantly; peripheral mechanisms are probably more important in episodic TTH, whereas central pain mechanisms are pivotal in chronic TTH (5). Thirdly, treatment differs between the subtypes, with symptomatic and prophylactic treatment being more appropriate for episodic and chronic TTH, respectively. Therefore, a precise diagnosis is mandatory and should be established by means of a headache diary for at least 4 weeks.

In general, non-pharmacological management should always be part of the treatment. With respect to pharmacological management, the general rule is that patients with episodic TTH are treated with symptomatic (acute) drugs, while prophylactic drugs should be considered in patients with very frequent episodic or chronic TTH. Analgesics are often ineffective in patients with chronic TTH. Furthermore, their frequent use increases risk of toxicity, as well as of medication overuse headache.

This chapter is based on treatment guidelines for TTH (6) and tries to summarize the knowledge of this very frequent but poorly studied headache disorder.

Epidemiology

The lifetime prevalence of TTH was about 78% in a population-based study in Denmark with the majority having episodic infrequent TTH without a specific need of medical attention (7). Twenty-four to 37% had TTH several times a month, 10% had it weekly, and 2–3% of the population had chronic TTH usually lasting for the greater part of a lifetime (8,9). In more recent studies, the prevalence figures for chronic TTH are lower, for example 0.5% for Germany (10), which is the consequence of the introduction of chronic migraine in the IHS classification.

The female-to-male ratio of TTH is 5:4 indicating that, unlike migraine, women are only slightly more affected than men (11,12). The average age of onset of TTH is higher than in migraine, namely 25–30 years in cross-sectional epidemiological studies (9). The prevalence peaks between the age of 30–39 years and decreases slightly with age. Poor self-rated health, inability to relax after work, and sleeping few hours per night have been reported as risk factors for developing TTH (8).

A review of the global prevalence and burden of headaches (12) showed that disability caused by TTH as a burden of society is greater than that by migraine, which indicates that the overall costs of TTH are greater than those of migraine. Two Danish studies have shown that the number of workdays missed in the population was three times higher for TTH than for migraine (9,13), and a US study also found that absenteeism due to TTH is considerable (14). The burden is particularly high for the minority who have substantial and complicating comorbidities (15).

Clinical aspects

TTH is characterized by a bilateral, dull pain of mild-to-moderate intensity, occurring either in short episodes of variable duration or continuously. The headache is not associated with autonomic features. In the chronic form, however, only one out of photophobia and phonophobia or mild nausea is accepted (**Box 29.1**). Owing to the lack of accompanying symptoms and the relatively mild pain intensity, patients are rarely severely incapacitated by their pain. TTH is the most featureless of the primary headaches, and because many secondary headaches may mimic TTH, a diagnosis of TTH requires exclusion of symptomatic headache disorders (see Chapters 38, 39, 46, and 47).

The diagnosis of TTH is based on the patient's history and a normal neurological examination. A correct diagnosis should be assured by a headache diary recorded over at least 4 weeks.

Box 29.1 Diagnostic criteria of tension-type headache according to the International Headache Society classification

2.1 Infrequent episodic tension-type headache

- **A** At least 10 episodes occurring on < 1 day per month on average (< 12 days per year) and fulfilling criteria B–D.
- **B** Headache lasting from 30 minutes to 7 days.
- **C** At least two of the following four characteristics:
  - **1** Bilateral location
  - **2** Pressing/tightening (non-pulsating) quality
  - **3** Mild or moderate pain intensity
  - **4** Not aggravated by routine physical activity such as walking or climbing stairs.
- **D** Both of the following:
  - **1** No nausea or vomiting
  - **2** No more than one of photophobia or phonophobia.
- **E** Not better accounted for by another ICHD-3 diagnosis.

2.2 Frequent episodic tension-type headache.

As 2.1 except for:

- **1** At least 10 episodes occurring on 1–14 days/month on average for > 3 months (≥ 12 and < 180 days per year) and fulfilling criteria B–D.

2.3 Chronic tension-type headache.

As 2.1 except for:

- **1** Headache occurring on ≥ 15 days per month on average for > 3 months (≥ 180 days per year), fulfilling criteria B–D.
- **2** Lasting hours to days, or unremitting.
- **3** Both of the following:
  - **1** No more than one of photophobia, phonophobia, or mild nausea.
  - **2** Neither moderate or severe nausea or vomiting.

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The most relevant diagnostic problem is to differentiate between TTH and mild migraine. If the headache is strictly unilateral, cervicogenic headache should also be considered (16). The diary may also reveal triggers and medication overuse, and it will establish the baseline against which to measure the efficacy of treatment. Identification of a high intake of analgesics is essential because medication overuse requires specific treatment. Diagnostic procedures, in particular brain imaging, is necessary if secondary headache is suspected (e.g. the headache characteristics are untypical), if the course of headache attacks changes, or if persistent neurological or psychopathological abnormalities are present.

Patients with chronic TTH have a high level of neuroticism and psychological distress. This can be either a primary or a secondary effect related to the premorbid psyche or caused by the chronic pain (17). Significant comorbidity such as anxiety or depression should be identified and treated concomitantly. Poor compliance with prophylactic treatment might be a problem in chronic TTH. It should be explained to the patient that frequent TTH only seldom can be cured, but that a meaningful improvement can be obtained with the combination of drug and non-drug treatment. It should be noted that chronic TTH almost always evolves from episodic TTH and does not begin de novo.

Patients with TTH need more sleep than healthy controls and might be relatively sleep deprived. Inadequate sleep may also contribute to increased pain sensitivity and headache frequency in TTH (18). However, no link between TTH and sleep apnoea syndrome could be detected (19).

If patients fulfil the criteria of both episodic migraine and chronic TTH, chronic migraine should be diagnosed according to the IHS criteria (see Chapter 31). Another problem might be to differentiate between chronic TTH and new daily persistent headache (NDPH) (see Chapter 30). If patients fulfil the criteria for NDPH, this should be the default diagnosis.

Pathophysiology

The exact pathophysiology of TTH is still not clarified. Despite several experimental studies, a precise explanation of pain processing in TTH is still missing. Meanwhile, it is obvious that episodic and chronic TTH do not share the same underlying pain processing (20). While chronic TTH seems to be a disturbance of the control of central pain processing, episodic TTH can be linked to increased peripheral pain perception and increased muscle tone, the latter being primary or secondary.

The tenderness of pericranial myofascial tissues and number of myofascial trigger points are considerably increased in patients with TTH. Mechanisms responsible for the increased myofascial pain sensitivity have been studied extensively. Peripheral activation or sensitization of myofascial nociceptors could play a role in causing increased pain sensitivity, but firm evidence for a peripheral abnormality is still lacking. Peripheral mechanisms are most likely of major importance in episodic TTH. Sensitization of pain pathways in the central nervous system due to prolonged nociceptive stimuli from pericranial myofascial tissues seem to be responsible for the conversion of episodic to chronic TTH (21,22). In chronic TTH, a significant decrease of grey matter in pain processing brain areas has been reported (23).

Acute drug treatment of tension-type headache

Acute drug therapy refers to the treatment of single headache attacks in patients with episodic or chronic TTH. Most headaches in patients with episodic TTH are mild to moderate, and the patients can often self-manage by using simple analgesics such as paracetamol or acetylsalicylic acid (ASA) or non-steroidal anti-inflammatory drugs (NSAIDs). The efficacy of simple analgesics tends to decrease with the increasing frequency of the headaches. In patients with chronic TTH, simple analgesics are usually ineffective and should be used with caution because of the risk of medication overuse headache at a regular intake of simple analgesics for more than 14 days a month, or triptans or combination analgesics for more than 9 days a month. Other interventions such as non-drug treatments and prophylactic pharmacotherapy should be considered.

The effect of acute drugs in TTH has been examined in many studies, and these have used many different methods for measurement of efficacy. The IHS guideline for drug trials in TTH recommends freedom from pain after 2 hours as the primary efficacy measure (6). This has been used in some studies, while many older studies used other efficacy measures such as pain intensity difference, time to meaningful relief, and so on. This makes comparison of results between studies difficult.

Simple analgesics and NSAID

Paracetamol 1000 mg was significantly more effective than placebo in most (24–31), but not all (32,33), trials, while three trials found no significant effect of paracetamol 500–650 mg compared with placebo (30,32,34).

Aspirin has consistently been reported more effective than placebo in doses of 1000 mg (30,35,36), 500–650 mg (30,35,37,38), and 250 mg (35). One study found no difference in efficacy between solid and effervescent aspirin (38).

Ibuprofen 800 mg (37), 400 mg (26,28,32,37,39,40), and 200 mg (41) are more effective than placebo, as are ketoprofen 50 mg (32,41), 25 mg (27,33,41), and 12.5 mg (33). One study could not demonstrate a significant effect of ketoprofen 25 mg, possibly owing to a low number of patients (32). Diclofenac 25 mg and 12.5 mg have been reported to be effective (40), while there have been no trials of the higher doses of 50–100 mg. Naproxen 375 mg (29) and 550 mg (34,42), and metamizole 500 mg and 1000 mg (36), have also been demonstrated effective. The latter drug is not available in many countries, because it carries a minimal (if at all) risk of agranulocytosis. Treatment with intramuscular injection of ketorolac 60 mg in an emergency department has also been reported to be effective (43).

There have only been a few studies investigating the optimal dose for drugs in the acute treatment of TTH. One study demonstrated a significant dose–response relationship of ASA, with 1000 mg being superior to 500 mg and 500 mg being superior to 250 mg (35). Ketoprofen 25 mg tended to be more effective than 12.5 mg (33), while another study found very similar effects of ketoprofen 25 mg and 50 mg (41). Paracetamol 1000 mg seems to be superior to 500 mg, as only the former dose has been demonstrated to be effective. In the face of a lack of evidence, the most effective dose of a drug well tolerated by a patient should be chosen. Suggested doses are presented in Table 29.1.

Five studies reported an NSAID to be significantly more effective than paracetamol (26,28,32–34), while three studies could not demonstrate a difference (27,29,30). Five studies have compared the efficacy of different NSAIDs without demonstrating a clear superiority of any particular drug (36,37,40,41,44).

With respect to parenteral acute treatment, metamizole, chlorpromazine, and metoclopramide showed evidence for efficacy in TTH; the combination of metoclopramide and diphenhydramine was superior to ketorolac; the following medications were not more effective than placebo: mepivacaine, meperidine and promethazine, and sumatriptan (45).

A thorough review of the acute drug treatment of TTH could not detect any difference in adverse events between paracetamol and NSAIDs, or between these drugs and placebo (46). However, it is well known that NSAIDs have more gastrointestinal side effects than paracetamol, while the use of large amounts of paracetamol may cause liver damage. Of the NSAIDs, ibuprofen seems to have the most favourable side effect profile (46).

Table 29.1 Drugs for the acute treatment of tension-type headache (TTH).

Substance	Dose	Comment
Ibuprofen	200–800 mg	Gastrointestinal side effects, risk of bleeding
Ketoprofen	25 mg	Side effects as for ibuprofen
Acetylsalicylic acid	500–1000 mg	Side effects as for ibuprofen
Naproxen	375–550 mg	Side effects as for ibuprofen
Diclofenac	12.5–100 mg	Side effects as for ibuprofen, only doses of 12.5–25 mg tested in TTH
Paracetamol	1000 mg	Less risk of gastrointestinal side effects than with NSAIDs

There is sparse evidence for optimal doses. The most effective dose of a drug well tolerated by a patient should be chosen. NSAID, non-steroidal anti-inflammatory drug.

Combination analgesics

The efficacy of simple analgesics and NSAIDs is increased in combination with caffeine 64–200 mg (24,26,47–49). One comparative study examined the efficacy of the combination of paracetamol with codeine and showed a significantly better efficacy than placebo and a similar efficacy to ASA (50). Combinations of simple analgesics with codeine or barbiturates, however, are not recommended, because these drugs increase the risk of medication overuse headache (51).

Miscellaneous drugs

Triptans have been reported to be effective for the treatment of interval headaches (52), which are most likely mild migraine attacks (53). Triptans most likely do not have a clinically relevant effect in patients with TTH (54,55) and cannot be recommended. Muscle relaxants have not been demonstrated to be effective in episodic TTH. The use of opioids increases the risk of developing medication overuse headache (51). Opioids are not recommended for the treatment of TTH.

Conclusions

Simple analgesics and NSAIDs are drugs of first choice in the acute treatment of TTH (Table 29.1). Paracetamol 1000 mg is probably less effective than the NSAID but has a better gastric side effect profile (56). Ibuprofen 400 mg may be recommended as the drug of first choice among the NSAIDs because of a favourable gastrointestinal side effect profile compared with other NSAIDs (56). Combination analgesics containing caffeine are more effective than simple analgesics or NSAIDs alone but are regarded by some experts to be more likely to induce medication overuse headache. Physicians should be aware of the risk of developing medication overuse headache as a result of frequent and excessive use of all types of analgesics in acute treatment. Triptans, muscle relaxants, and opioids do not play a role in the treatment of TTH.

Although simple analgesics and NSAIDs are effective in episodic TTH, the degree of efficacy has to be put in perspective. For example, the proportion of patients being pain free 2 hours after treatment with paracetamol 1000 mg, naproxen 375 mg, and placebo were 37%, 32%, and 26%, respectively (29). The corresponding rates for paracetamol 1000 mg, ketoprofen 25 mg, and placebo were 22%, 28%, and 16%, respectively, in another study with 61%, 70%, and 36% of patients reporting a worthwhile effect (27). Thus, efficacy is modest, and there is clearly a need for better acute treatment options of episodic TTH.

Prophylactic drug treatment of tension-type headache

Prophylactic pharmacotherapy should be considered in patients with chronic or very frequent episodic TTH. Comorbid disorders such as obesity or depression should be taken into account. For many years, the tricyclic antidepressant amitriptyline has been used. More lately, other antidepressants, NSAIDs, muscle relaxants, anticonvulsants, and botulinum toxin have been tested in chronic TTH. The effect of prophylactic drugs has been examined only in very few placebo-controlled studies, which have used different methods for measurement of efficacy. The IHS guidelines for drug trials in TTH recommend days with TTH or area-under-the-headache curve (AUC) as primary efficacy measure (6). These parameters have been used in some studies, while other studies have used other efficacy measures such as pain reduction from baseline, headache intensity, and so on. This makes comparison of results between studies difficult.

Amitriptyline

Lance and Curran (57) reported amitriptyline 10–25 mg q8h to be effective, while Diamond and Baltes (58) found amitriptyline 10 mg daily but not 60 mg daily to be effective. Amitriptyline 75 mg daily was reported to reduce headache duration in the last week of a 6-week study (59), while no difference in effect size between amitriptyline 50–75 mg daily or amitriptylinoxide 60–90 mg daily and placebo was found in one study (60). Bendtsen et al. (61) showed that amitriptyline 75 mg daily reduced the AUC (calculated as headache duration times headache intensity) by 30% versus placebo, which was highly significant. Holroyd et al. (62) treated patients with antidepressants (83% took amitriptyline median dose 75 mg daily; 17% took nortriptyline median dose 50 mg daily) and compared this with stress management therapy and with a combination of stress management and antidepressant treatment. After 6 months, all three treatments reduced the headache index by approximately 30% more than placebo, which was highly significant.

Other antidepressants

The tricyclic antidepressant clomipramine 75–150 mg daily (63) and the tetracyclic antidepressant mianserin 30–60 mg daily (63) have been reported more effective than placebo. Interestingly, some of the newer, more selective antidepressants with action on serotonin and noradrenaline seem to be as effective as amitriptyline with the advantage of better tolerability. The noradrenergic and specific serotonergic antidepressant mirtazapine 30 mg daily reduced the headache index by 34% more than placebo in difficult-to-treat patients without depression, including patients who had not responded to amitriptyline (64). The efficacy of mirtazapine was comparable to that of amitriptyline reported by the same group (61). A systematic review concluded that the two treatments may be equally effective for the treatment of chronic TTH (65). The serotonin and noradrenaline reuptake inhibitor venlafaxine 150 mg daily (66) reduced headache days from 15 to 12 per month in a mixed group of patients with either frequent episodic or chronic TTH. Low-dose mirtazapine 4.5 mg daily alone or in combination with ibuprofen 400 mg daily was not effective in chronic TTH. The selective serotonin reuptake inhibitors (SSRI) citalopram (61) and sertraline (67) have not been found more effective than placebo. SSRIs have been compared with other antidepressants in six studies. These studies were reviewed in a Cochrane analysis that concluded that SSRIs are less efficacious than tricyclic antidepressants for the treatment of chronic TTH (68).

Miscellaneous agents

There have been conflicting results for treatment of TTH with the muscle relaxant tizanidine (69,70). The *N*-methyl-D-aspartate antagonist memantine was not effective (71). Botulinum toxin has been extensively studied in chronic TTH with negative results in all placebo-controlled trials (72). There is some evidence from an open-label trial that topiramate is also efficacious in chronic TTH (73). The prophylactic effect of daily intake of simple analgesics has not been studied in trials on chronic TTH, but explanatory analyses indicated that ibuprofen 400 mg daily was not effective in one study (74). On the contrary, ibuprofen increased headache compared with placebo, indicating a possible early onset of medication overuse headache (74).

Conclusions

Amitriptyline has a clinically relevant prophylactic effect in patients with chronic TTH and should be drug of first choice (Table 29.2). Mirtazapine or venlafaxine are probably effective, while the older tricyclic and tetracyclic antidepressants clomipramine, maprotiline, and mianserin may be effective. A recent systematic review (65) concluded that amitriptyline and mirtazapine are the only drugs that can be considered proven beneficial for the treatment of chronic TTH. However, the last search was performed in 2007 before publication of the study on venlafaxine (66).

Amitriptyline should be started at low dosages (10 mg daily) and titrated by 10 mg weekly until the patient has either good therapeutic effect or side effects. It is important that patients are informed about the independent action on pain by antidepressants. The maintenance dose is usually 30–75 mg daily administered 1–2 hours before bedtime to circumvent any sedative adverse effects. The effect is not related to the presence of depression (61). A significant effect of amitriptyline may be observed in the first week on the therapeutic dose (61). It is therefore advisable to change to other prophylactic therapy if the patient does not respond after 4 weeks on the maintenance dose. The side effects of amitriptyline include dry mouth, drowsiness, dizziness, obstipation, and weight gain. Mirtazapine, of which

Table 29.2 Drugs for the prophylactic treatment of tension-type headache (for side effects see text).

Substance	Daily dose (mg)
Drug of first choice	
Amitriptyline	30–75
Drugs of second choice	
Mirtazapine	30
Venlafaxine	75–150
Drugs of third choice	
Clomipramine	75–150
Maprotiline	75
Mianserin	30–60

the major side effects are drowsiness and weight gain, or venlafaxine, of which the major side effects are nausea, dizziness, and loss of libido, should be considered if amitriptyline is not effective or not tolerated. Discontinuation should be attempted every 6–12 months. The physician should keep in mind that the efficacy of preventive drug therapy in TTH is often modest, and that the efficacy should outweigh the side effects.

Non-pharmacologic treatment of tension-type headache

Patient education

Non-drug management should be considered for all patients with TTH and is widely used. However, the scientific evidence for the efficacy of most treatment modalities is sparse. The very fact that the physician takes the problem seriously may have a therapeutic effect, particularly if the patient is concerned about serious disease, for example a brain tumour, and can be reassured by thorough examination. A detailed analysis of trigger factors should be performed, as avoidance of trigger factors may have a long-lasting effect. The most frequently reported triggers for TTH are stress (mental or physical), irregular or inappropriate meals, high intake or withdrawal of coffee and other caffeine-containing drinks, dehydration, sleep disorders, too much or too little sleep, reduced or inappropriate physical exercise, psycho-behavioural problems, as well as variations during the female menstrual cycle and hormonal substitution (75,76). Most of triggers are self-reported and so far none of the triggers has been systematically tested.

Information about the nature of the disease is important. It can be explained that muscle pain can lead to a disturbance of the brain's pain-modulating mechanisms, so that normally innocuous stimuli are perceived as painful, with secondary perpetuation of muscle pain and risk of anxiety and depression. Moreover, the patient should be explained that the prognosis in the longer run is favourable, as approximately half of all individuals with frequent or chronic TTH had remission of their headaches in a 12-year epidemiological follow-up study (13).

Psycho-behavioural treatments

A large number of psycho-behavioural treatment strategies have been used to treat chronic TTH. Electromyography (EMG) biofeedback, cognitive–behavioural therapy (CBT), and relaxation training have been investigated the most. However, only a few trials have been performed with sufficient power and clear outcome measures (77).

The aim of EMG biofeedback is to help the patient recognize and control muscle tension by providing continuous feedback about muscle activity. Sessions typically include an adaptation phase, a baseline phase, a training phase, where feedback is provided, and a self-control phase, where the patient practices controlling muscle tension without the aid of feedback. A recent review including 11 studies concluded that because of low power there is conflicting evidence to support or refute the effectiveness of EMG biofeedback versus placebo or any other treatments (77). However, a recent extensive and thorough meta-analysis including 53 studies concluded that biofeedback has a medium-to-large effect. The effect was found to be long-lasting and enhanced by combination with relaxation therapy (78). The majority of studies included employed EMG biofeedback. It was not possible to draw reliable conclusions as to whether the effect differed between patients with episodic and chronic TTH.

The aim of CBT is to teach the patient to identify thoughts and beliefs that aggravate headache. These thoughts are then challenged, and alternative adaptive coping self-instructions are considered. One study found CBT, treatment with tricyclic antidepressants, and a combination of the two treatments better than placebo with no significant difference between treatments (62), while another study reported no difference between CBT and amitriptyline (79). CBT may be effective, but there is no convincing evidence (65).

The goal of relaxation training is to help the patient recognize and control tension as it arises in the course of daily activities. During the training, the patient sequentially tenses and then releases specific groups of muscles throughout the body. Later stages involve relaxation by recall, association of relaxation with a cue word, and maintaining relaxation in muscles not needed for current activities. Relaxation training has been compared with no treatment, waiting list control, or with other interventions. A recent review concluded that there is conflicting evidence that relaxation is better than no treatment, waiting list, or placebo (77).

Mindfulness-based therapy was also studied in a randomized, controlled trial and showed a significant improvement of chronic TTH versus a waiting list (80).

EMG biofeedback has an effect in TTH, while CBT and relaxation training may have an effect in TTH, but at this moment there is no convincing evidence to support this. These treatments are relatively time-consuming, but, unfortunately, there are no guidelines regarding which psycho-behavioural treatment to choose for the individual patient. Therefore, until scientific evidence is provided, it is assumed that CBT will be most beneficial for patients in whom psycho-behavioural problems or affective distress play a major role, while biofeedback or relaxation training may be preferable for tense patients.

Physical therapy

Physical therapy is widely used for the treatment of TTH and includes improvement of posture, massage, spinal manipulation, oromandibular treatment, exercise programmes, hot and cold packs, ultrasound, and electrical stimulation, but the majority of these modalities have not been properly evaluated. Active, but not passive, treatment strategies are generally recommended (81). Carlsson et al. (82) reported a better effect of physiotherapy than acupuncture. A controlled study (83) combined various techniques such as massage, relaxation, and home-based exercises, and found a modest effect. Adding craniocervical training to classical physiotherapy was found to be better than physiotherapy alone (84). A recent study found no significant long-lasting differences in efficacy among relaxation training, physical training, and acupuncture (85). Spinal manipulation had no effect in episodic TTH (86) and no convincing effect in chronic TTH (87–89), whereas manual therapy was reported to be better than standard care by a general practitioner (90). There is no firm evidence for efficacy of therapeutic touch, cranial electrotherapy, or transcutaneous electrical nerve stimulation (91).

It can be concluded that there is a huge contrast between the widespread use of physical therapies and the lack of robust scientific evidence for efficacy of these therapies, and that further studies of improved quality are necessary to either support or refute the effectiveness of physical modalities in TTH (91–93).

Acupuncture and nerve blocks

The prophylactic effect of acupuncture has been investigated in several trials in patients with frequent episodic or chronic TTH. Two trials reported better effect of acupuncture than basic care or waiting list but no better effect of Chinese acupuncture versus sham acupuncture (94,95), while a recent Cochrane analysis concluded that there was overall a slightly better effect from acupuncture than from sham acupuncture based on the results of five trials (96). Four trials compared acupuncture with physiotherapy (82,85,97), relaxation (85), or a combination of massage and relaxation (98); these trials suggest slightly better results for some outcomes with the latter therapies according to the recent Cochrane analysis (96,99). A meta-analysis using other criteria for inclusion of studies (100) and a review (65) concluded that there is no evidence for efficacy of acupuncture in TTH. Together, the available evidence suggests that acupuncture could be a valuable option for patients suffering from frequent TTH, but more research is needed before final conclusions can be made.

A recent study reported no effect of greater occipital nerve block in patients with chronic TTH (101).

Recommendations

Non-drug management should always be considered in TTH treatment, although the scientific background is limited. Information, reassurance, and identification of trigger factors may be rewarding. EMG biofeedback has documented efficacy in TTH, while CBT and relaxation training most likely are effective, but there is no convincing evidence. Physical therapy and acupuncture may be valuable options for patients with frequent TTH, but there is no robust scientific evidence for efficacy.

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30

New daily persistent headache

Kuan-Po Peng, Matthew S. Robbins, and Shuu-Jiun Wang

Introduction

History of new daily persistent headache

The term new daily persistent headache (NDPH) was first used in an abstract by Vanast in 1986 (1). In this initial description, the headache was described as occurring daily since the first day it began, and secondary causes, including psychological tension, trauma, or pre-existing headache disorders, had to be excluded before making a diagnosis of NDPH. Vanast reported 45 patients (26 females, 19 males), most in their twenties to forties. The headache features were heterogeneous, including steady headache (72%), pounding headache (28%), and unilateral headache (38%); associated symptoms were rather common, including nausea (53% of females, 57% of males), photophobia (42% of females, 26% of males), and phonophobia (53% of females, 21% of males). The overall prognosis was good: more than 70% of the patients were free from headache by the 2-year follow-up. The positive outcome in Vanast's series was quite different from the results of later series—NDPH was later considered very resistant to treatment.

Evolving diagnostic criteria for new daily persistent headache

In early series, a diagnosis of NDPH was mostly made according to the clinical syndrome of a 'new daily persistent' headache, which therefore encompassed both idiopathic and secondary aetiologies (1–4). As both the clinical features and the aetiological diagnoses were varied, this led to a heterogeneous group of patients. In 1994, Silberstein and Lipton et al. (5) proposed the first diagnostic criteria for NDPH, defining it as a subtype of chronic daily headache (CDH), which is a headache exceeding 4 hours per day for > 15 days per month. In addition, the onset of NDPH is within ≤ 3 days, and secondary headaches and a previous history of tension-type headache (TTH) or migraine preclude the diagnosis of NDPH (5). The Silberstein and Lipton (S-L) criteria clearly defined the onset and duration of the headache, but in this definition NDPH is not necessarily daily or persistent. In 2004, NDPH was listed as a primary headache disorder by the International Headache Society in the International Classification of Headache Disorders, 2nd edition (ICHD-2) (6). In the ICHD-2 criteria, the headache features of NDPH were clearly defined for the first time as similar to TTH instead of being migrainous. In addition, the daily and persistent characteristics of NDPH were put back compared to the S-L criteria. However, many clinical series identified a certain proportion of patients who otherwise fulfilled the diagnostic criteria of NDPH, except for the TTH-like headache features (7–10). Thus, in the recently released third edition of the ICHD (ICHD-3), patients who have migrainous headache are no longer excluded. Moreover, patients with prior infrequent migraine or TTH are also allowed in the absence of increasing frequency of a pre-existing headache before the onset of NDPH, but a strict cut-off of baseline monthly headache days prior to NDPH onset remains absent (Box 30.1) (11).

Epidemiology

There are few epidemiological studies of NDPH. Primary CDH affects 4% of the general population (12,13), and up to 80% of patients in tertiary headache clinics (5,14,15). Four subtypes of CDH were originally proposed by Silberstein and Lipton et al. (5) and later adopted in ICHD-2 (6), including chronic migraine (CM), chronic tension-type headache (CTTH), hemicrania continua (HC), and NDPH. In patients with CDH from tertiary centres, NDPH might be more common in the paediatric (0.9–35%) (16–18) than in the adult population (2.5–10.8%) (10,14). However, in community-based studies, NDPH is rarely found. In Spain, the 1-year prevalence of NDPH is 0.1% in those aged > 14 years (13); in Norway, the 1-year prevalence is as low as 0.03% in those aged 30–44 years (19). In Taiwan, of 7900 adolescents aged 12–14 years, 122 patients with CDH were diagnosed, but none of them had NDPH (20). It must be noted that most of the aforementioned studies used ICHD-2 criteria, which are more restrictive. Therefore, more studies are needed to re-evaluate the prevalence of NDPH using the newer and more permissive ICHD-3 criteria.

Triggers to the onset of new daily persistent headache and potential pathological links

Reported triggers that are associated with NDPH onset are miscellaneous and often absent. In a large NDPH series (n = 97) by Rozen

Box 30.1 Criteria for new daily persistent headache

A Persistent headache fulfilling criteria B and C.
B Distinct and clearly-remembered onset, with pain becoming continuous and unremitting within 24 hours.
C Present for > 3 months.
D Not better accounted for by another ICHD-3 diagnosis.

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(21), more than 50% of the patients recalled no specific triggers. The various triggers that have been reported with NDPH may provide potential links to the underlying disease mechanism.

Infection or flu-like episodes

An early case–control study indicated that viral infection might be a trigger to the onset of NDPH. Diaz-Mitoma et al. (2) reported that 27 of 32 (84%) patients with NDPH versus eight of 32 (25%) controls, have evidence of active Epstein–Barr virus (EBV) infection, defined by EBV secretion and/or early antigen titre > 1:32. This cohort of NDPH averaged 27.9 years in age, featured a majority (84%) of women, and mostly presented with bilateral headaches (81%) (2). In this study, NDPH was defined as a new-onset headache that persisted for at least 1 month. Secondary causes of endocrine, autoimmune, or neoplastic disorders were excluded; however, other NDPH mimics, including high-/low-pressure headaches, chronic meningitis, or vascular lesions, were not rigorously excluded. A subsequent large study reported 108 patients with secondary NDPH, defined as (i) bilateral daily headache lasting up to 8 weeks in the absence of a previous history of a primary headache disorder; (ii) laboratory evidence of active infection; and (iii) relief of headache after proper antibiotic treatment. In this series, only four patients (3.7%) were positive for EBV, but other systemic infections were common, including *Salmonella* in 28 (25.9%), and *Escherichia coli* in 16 (14.8%). In a study by Rozen (21), who utilized ICHD-3 diagnostic criteria, infection or flu-like illness was the most common trigger (22%) in 97 patients with NDPH. The triggers did not differ between men and women (21). All these studies provided evidence that NDPH-like headaches might be a rather common symptom in those with an active systemic infection, regardless of the pathogen.

Two studies on the adult population showed peaks of NDPH onset in March/April and September (9,23). One recent study on the paediatric population showed peaks of NDPH onset in January and September (22), both at the start of a new semester. These studies suggest a potential seasonal infectious or environmental link.

Stressful life events

Prior to the onset of NDPH, 9–26% of patients recall stressful life events (7,9,10,21,23). The direct mechanism by which stressful life events could lead to NDPH is unknown; however, the occurrence of a major life event is a known risk factor for CDH. Patients with CDH, versus controls, were more likely to report stressful life events in the year before the diagnosis of CDH (24). In animal models, chronic stress exposure produced hyperalgesia; central sensitization remains the most accepted mechanism how an episodic headache progresses to CDH (25). Nevertheless, stressful life events are easy to be recalled, but the causality between the event and the headache onset is difficult to ascertain.

Tumour necrosis factor-α and NDPH

Tumour necrosis factor (TNF)-α is a pro-inflammatory cytokine. Rozen and Swidan (26) examined the level of TNF-α in serum and cerebrospinal fluid (CSF) in 20 patients with primary NDPH, 16 patients with CM, and two patients with post-traumatic headache. The CSF TNF-α level was elevated in 19 of 20 patients with NDPH, 16 of 16 patients with CM, and two of two patients with post-traumatic headache; however, the serum TNF-α level was mostly normal (elevated in five of 14 patients with NDPH patients, zero of 16 patients with CM, and one of two with post-traumatic headache) (26). The discrepancy between CSF and serum levels of TNF-α potentially suggested intrathecal rather than systemic inflammation. In animal models, both infection and stress activate glial cells and increase cytokine production, including TNF-α (27,28). TNF-α is known to increase the production of calcitonin gene-related peptide, a neurotransmitter associated with headache and migraine (29). The role of TNF-α provides a link to how some triggers may result in NDPH or even other chronic headache disorders, including CM and post-traumatic headache, but its specificity for the individual forms of CDH is not clear.

Hypermobility syndrome

Rozen et al. (30) reported that 11 of 12 patients with NDPH had cervical spine joint hypermobility and 10 of 12 had widespread joint hypermobility, as evaluated by physical therapists using the Beighton score, but there was no control group in this study (30). In patients with hypermobility, a diagnosis of NDPH must be prudently made as a hypermobility syndrome can also be associated with spontaneous intracranial hypotension (31), which possibly mimics NDPH in clinical presentation.

Other triggers

In some NDPH cohorts, several rare other triggers were reported. Li and Rozen (23) reported that 12% of their patients had undergone surgery before the onset of NDPH. In a later series by Rozen (21), he found that all of the patients who developed NDPH after surgery had been intubated during surgery, and speculated a cervicogenic link. Robbins et al. (9) described others as triggers for NDPH in a series of 71 patients: menarche ($n = 3$), tapering of antidepressants ($n = 2$), and vaccination ($n = 1$). As all reported cohorts were retrospective, these rare triggers might be life events easily recalled and thus causality to NDPH is questionable.

Triggers in a paediatric population

Most of the aforementioned studies included adult patients only. Mack (32) reported on possible causes in a paediatric population, including both primary and secondary NDPH. He identified 40 paediatric patients with NDPH. Seventeen (43%) of them reported a febrile disease at the onset of NDPH, and in nine of 17 an EBV infection was confirmed. Minor head trauma was reported in another nine patients, but this raised the concern of post-traumatic headache and not NDPH. Other causes in this study included idiopathic intracranial hypertension, surgery, and high-altitude climbing. Only five patients (12.5%) recalled no specific predisposing events.

Pathophysiological mechanisms of NDPH

There is no consensus or solid evidence base to embrace any of the hypothesized pathophysiological mechanisms that have been proposed to date. Different studies used different diagnostic criteria for NDPH. Primary NDPH and secondary NDPH were both included in different studies. Moreover, primary NDPH might rather be a syndrome than a specific disease, as Goadsby proposed (33); thus, multiple underlying mechanisms might co-exist. Therefore, a consensus in clinical diagnostic criteria might be the first step for further aetiological exploration.

Clinical presentation of new daily persistent headache

Headache features

Despite the diverse headache features of NDPH in different clinical series, one key feature remains: most patients with NDPH present with an abrupt onset of a persistent or near-persistent headache on one specific day. Although the ICHD-2 criteria allowed a 72-hour window of onset (6), patients with an onset of fluctuating headache that becomes persistent within 72 hours might represent a minority of patients with NDPH, and the ICHD-3 criteria no longer allow for this variability in onset (11). For many clinicians, whether the patient could recall the specific day or circumstances of the headache onset remains crucial in the diagnosis of NDPH. In our experience, the circumstances of the headache onset might be usual: one patient recalled the headache started when he was sitting on the couch watching television. Instead, specific circumstances at the onset of headache should raise the concern of secondary headache diagnoses that mimic NDPH, i.e. an abrupt headache after sneezing or weight lifting would raise the concern of low-pressure headache due to CSF leakage after minor trauma.

A female predominance is reported in both adult (1.4–2.5:1) (1,9,10,23) and paediatric populations (1.8–2.9:1) (8,18), except for one Japanese study that reported a male predominance (1.3:1); this study used the more restrictive ICHD-2 criteria (7). The age at onset is wide, ranging from 6 to 76 years (8,9,23). Several earlier North American series reported a younger peak age at onset in women (10–35 years) (1,9,23) than in men (30–50 years) (1,23). On the contrary, two Asian studies reported a younger peak age at onset in men (10–30 years) (7,10) than in women (40–60 years) (10). A large-scale American study by Rozen (21) reported no obvious difference in age at onset between the sexes (21). The location of pain was most frequently over occipital and temporal regions (1,23). The pain is usually moderate to severe (82–100%) (7,9,10,23), bilateral (53–89%) (7–10,23), and pulsating (41–90%) (7,9,10,23). In addition, the headache is often associated with nausea (33–68%) (7–10,23), photophobia (45–69%) (8–10,23), and photophobia (41–63%) (8–10,23).

Migrainous features in NDPH

Although TTH features are clearly defined in the diagnostic criteria of NDPH in ICHD-2 (6), in most described cases, the headache could be very 'migrainous', even in those who follow the ICHD-2 criteria strictly (7,9,10). Owing to the frequent migrainous features (moderate or severe headache, pulsating characteristics, nausea, photophobia, and phonophobia) in patients with NDPH, Kung et al. (8) proposed revised criteria that do not exclude those with prominent migrainous features. This concept was followed in subsequent studies despite slightly differing details (9,10,34). Thus, in ICHD-3, headache features, either migrainous or TTH-like, are no longer restricted (11).

Pre-existing headache disorders before the diagnosis of NDPH

A pre-existing headache disorder before the diagnosis of NPDH raises the concern of whether the new persistent headache is a de novo NDPH or deterioration of a pre-existing headache disorder. In the literature, pre-existing headache disorders (TTH or migraine) before the diagnosis of NDPH are rather common (7–38%) (7,9,10,23). In addition, the headache features of NDPH seem irrelevant to the pre-existing headache features; that is, patients with a previous migraine diagnosis were no more likely to develop NDPH with migrainous features (9,10,34). In the S-L criteria, a pre-existing headache disorder is not allowed; however, the ICHD-2 or the ICHD-3 do not exclude those with a pre-existing headache disorder. There is no consensus of a maximum frequency of pre-existing headaches allowed before the diagnosis of NDPH. However, greater prudence should be taken before making a diagnosis of NDPH if a baseline headache increased in frequency before NDPH onset, or the baseline headache is not infrequent.

Diagnosis of new daily persistent headache: possible mimics

Giving the current diagnostic criteria, NDPH cannot be diagnosed unless other headache disorders have been excluded properly. One must keep in mind that none of the clinical spectrum of symptoms is specific to NDPH. Thus, NDPH must be differentiated from any other headache disorder that occurs frequently or even persistently.

NDPH mimics: primary headaches

Of the primary headache disorders, CM and CTTH must be carefully explored and a history of increased frequency of pre-existing headache disorder must be scrutinized. In addition, HC should be excluded, as up to 18% of patients with NDPH may present with side-locked unilateral headache (10). Furthermore, cranial autonomic symptoms are also common in 12.9–27.5% of patients with NDPH (9). Thus, a trial of indomethacin up to 150 mg daily (in certain cases up to 225 mg daily) for up to 2 weeks should be administered to exclude HC in those with unilateral NDPH (35). Primary thunderclap headache may also present with a subsequent persistent residual headache, even though the initial explosive headache often lasts 1 hour to 10 days (6); however, with the better understanding of reversible cerebral vasoconstriction syndrome (RCVS), many of the patients, previously regarded as suffering from primary thunderclap headache were later diagnosed with RCVS. RCVS will be discussed later in NDPH mimics of secondary headaches. Lastly, nummular headache (see also Chapter 33), which is newly proposed as a primary headache disorder in ICHD-3 (11), could also be persistent, but the defining feature of pain over a fixed region of 2–6 cm in diameter is rarely reported in NDPH series (11).

NDPH mimics: secondary headaches

Any secondary headache disorder that can induce persistent headaches could mimic NDPH. A neurological examination could reveal certain secondary causes, such as space-occupying lesions in the brain; however, several NDPH mimics can only be detected when a specific examination and diagnostic work-ups have been performed (Figure 30.1).

Active and previous meningitis

As previously mentioned in the pathophysiology, occult central nervous system infection poses an important differential diagnosis of NDPH. Acute bacterial meningitis, presenting with neck stiffness, fever, and changes of consciousness, is not often confused with NDPH. However, the symptoms of certain chronic meningitides are less specific and could consist of only headaches, i.e. mycobacterial meningitis, fungal meningitis, or Mollaret's meningitis—commonly caused by herpes simplex virus type 2 (36). These occult infections can only be excluded with the help of a CSF analysis. Except for active meningitis, post-meningitis headache is another differential diagnosis. Headache attributed to past bacterial meningitis is listed in the ICHD-3 (11); however, persistent headache attributed to past viral meningitis is not a valid diagnosis in ICHD-3 (11). Except for being younger, those who developed headaches after resolution of meningitis did not differ from those without subsequent headache (37).

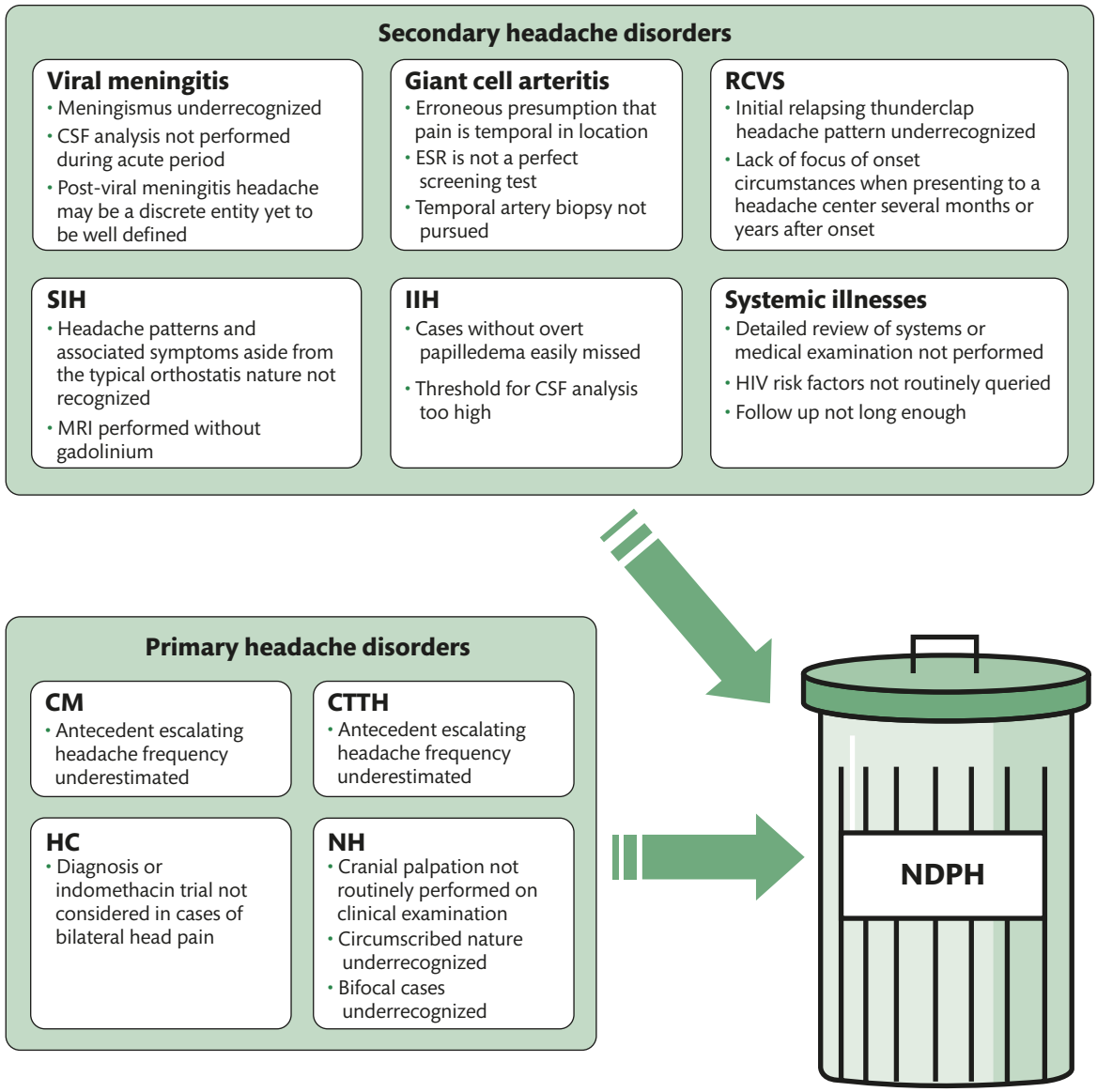
Secondary headache disorders
Viral meningitis
• Meningismus underrecognized
• CSF analysis not performed during acute period
• Post-viral meningitis headache may be a discrete entity yet to be well defined
Giant cell arteritis
• Erroneous presumption that pain is temporal in location
• ESR is not a perfect screening test
• Temporal artery biopsy not pursued
RCVS
• Initial relapsing thunderclap headache pattern underrecognized
• Lack of focus of onset circumstances when presenting to a headache center several months or years after onset
SIH
• Headache patterns and associated symptoms aside from the typical orthostatis nature not recognized
• MRI performed without gadolinium
IIH
• Cases without overt papilledema easily missed
• Threshold for CSF analysis too high
Systemic illnesses
• Detailed review of systems or medical examination not performed
• HIV risk factors not routinely queried
• Follow up not long enough
Primary headache disorders
CM
• Antecedent escalating headache frequency underestimated
CTTH
• Antecedent escalating headache frequency underestimated
HC
• Diagnosis or indomethacin trial not considered in cases of bilateral head pain
NH
• Cranial palpation not routinely performed on clinical examination
• Circumscribed nature underrecognized
• Bifocal cases underrecognized
NDPH

Figure 30.1 Secondary and primary headache disorders that may be overlooked when new daily persistent headache (NDPH) is diagnosed.

CSF, cerebrospinal fluid; ESR, erythrocyte sedimentation rate; RCVS, reversible cerebral vasoconstriction syndrome; SIH, spontaneous intracranial hypotension; MRI, magnetic resonance imaging; IIH, idiopathic intracranial hypertension; HIV, human immunodeficiency virus; CM, chronic migraine; CTTH, chronic tension-type headache; HC, hemicrania continua; NH, nummular headache.

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Idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH), also known as pseudotumour cerebri or benign intracranial hypertension, is an easily neglected cause of chronic daily headache (see also Chapter 39). It is usually seen in obese women of childbearing age. The most common symptoms are headache, papilloedema, and occasionally pulsatile tinnitus (38). Of note, around 5.3% of patients with IIH may present without papilloedema (39). Those without papilloedema are more likely to have photopsia, spontaneous venous pulsations, and a lower—albeit still elevated—CSF pressure than those with papilloedema. A detailed fundus and visual field examination by a neuro-ophthalmologist is suggested (39). Regarding the headache features, IIH could either mimic CM (40) or CTTH (41). Thus, in patients without papilloedema or other focal neurological deficits, it is impossible to differentiate IIH and NDPH according to clinical presentations. Moreover, both IIH and NDPH require a normal brain imaging study to exclude other diagnoses—although certain image findings are rather common in patients with IIH, especially bilateral transverse sinus stenosis (42), as identified on magnetic resonance venography (MRV). Thus, a spinal puncture to measure the opening pressure is crucial, but a single normal spinal tap does not exclude the possibility of intracranial hypertension as a certain proportion of patients have intermittent, instead of persistent, intracranial hypertension (43). Thus, prolonged monitoring of CSF pressure for 30 minutes or more, or repetitive tapping with multiple measurements, is suggested (44) in those with common risk factors of IIH to completely exclude the diagnosis of IIH.

Spontaneous intracranial hypotension

Spontaneous intracranial hypotension (SIH) is a rare headache disorder—albeit generally believed to be under-diagnosed (see also Chapter 38). SIH most often affects young and middle-aged adults and is twice as common in women than in men (45). The headache features of SIH share certain similarities to those of NDPH. Firstly, the headache usually starts on a specific day after a trivial trauma such as sneezing or taking a rollercoaster ride (46), or no obvious triggers are identified. Secondly, the headache usually occurs daily from the onset (47). Although SIH features an orthostatic headache, which disappears completely or improves greatly after lying supine and recurs within 15 minutes after standing up (6), the headache may evolve to be persistent with minor fluctuation after postural changes in time. Thus, taking a detailed history of the initial headache features at onset is important. Moreover, generalized connective tissue disease is a known predisposing factor to SIH (48–50), and one previous report identified that 11 of 12 patients with NDPH had cervical spine hypermobility syndrome—which is a feature of generalized connective tissue disorder (30). Thus, a relevant history of connective tissue disorder or hypermobility should raise concern for both diagnoses. Except for documentation of CSF hypotension through lumbar punctures, cranial MRI with and without contrast provides radiological evidence of CSF hypotension in a majority of patients of SIH, including (i) diffuse pachymeningeal enhancement; (ii) brain sagging; (iii) pituitary hyperaemia; and (iv) engorgement of venous structures (47). None of the above features should be seen in patients with NDPH. In addition, more evidence suggests magnetic resonance myelography might be a suitable alternative to visualize CSF leakage without creating a secondary leakage during the process of injecting contrast into the intradural space when performing computed tomography myelography (51).

RCVS

The key features of RCVS are recurrent thunderclap headaches and reversible segmental vasoconstriction of arterial branches of the circle of Willis (see also Chapter 49). The headache is usually so severe as to raise the concern of aneurysmal subarachnoid haemorrhage (SAH). Patients are mostly middle-aged women, but paediatric cases have also been reported (52). Recurrent thunderclap headaches remain for an average of 2 weeks; however, cerebral vasoconstriction may last up to 3–6 months, even after the resolution of the clinical symptoms (53). Although the median duration of each thunderclap headache is 3 hours, up to 50% of the patients experience a milder persistent headache at baseline during the interval of RCVS and sometimes mimicking or comorbid with migraine (54). In addition, 80% of the sufferers have known triggers for the occurrence of each thunderclap headache, including exertion, bathing, sex, and defaecation (55–57). Owing to the specific triggers, most of the patients remembered the exact day of headache onset, as seen in patients with NDPH. To consolidate the diagnosis of RCVS, cerebral magnetic resonance images including angiography and lumbar punctures—for the exclusion of occult SAH not detected on non-contrast computed tomography—remain the studies of choice.

Strictly speaking, RCVS rarely lasts for more than 3 months and thus seldom fulfils the diagnostic criteria of NDPH, despite similar clinical symptoms—a new-onset persistent headache (6). However, a study published in abstract form followed the long-term outcome of 16 patients with RCVS. Of the 14 patients successfully followed, CDH developed in six of the 14 (43%) patients after an average of 99 weeks of follow-up (58). A second preliminary study also noted long-term persistent headache in a subset of patients (n = 11/20) with RCVS (59). Thus, NDPH might be extremely difficult to differentiate from RCVS in this subgroup of patients without early diagnostic evaluation at the onset of headache. Moreover, 9–63% patients may develop transient or permanent neurological deficits (56,57,60), including posterior reversible encephalopathy syndrome (9–14%), cerebral infarction (4–54%), cortical SAH (22–34%), or intracerebral haemorrhage (6–20%) (56,57,60,61). These complications may result in prolonged headache, even after the resolution of RCVS.

Other secondary headache disorders

In patients > 50 years of age, giant cell arteritis (GCA) should always be considered in the differential diagnosis. More than half of patients with GCA complained of persistent and unremitting headache similar to NDPH (62). Moreover, the headache could be either unilateral or bilateral (62,63). An elevated erythrocyte sedimentation rate (ESR) is generally observed; however, up to 22.5% of patients present with a normal ESR at the beginning (64), although C-reactive protein may increase the diagnostic yield (65). Thus, temporal artery biopsy is recommended in patients suspected to have GCA (63). Other disorders, including various infection and neoplasms located in the head and neck, cervical artery dissections, vascular anomalies, or temporomandibular joint dysfunction, could also be considered if patients present with a compatible history of neurological findings.

Suggested diagnostic tests

A great number of diseases could mimic NDPH; in order to make a proper diagnosis, a detailed headache history is crucial. As with diagnosing any headache disorder, it is important to let the patient express the symptoms in open questions rather than jumping into some criteria-fitting closed questions. The physician should focus on how the headache started, although this might be rather difficult as many patients visit the clinic years after their headache onset. Further physical and neurological examinations follow the initial clues from the history taking. To properly exclude potential NDPH mimics, a brain image study, preferably MRI with and without contrast, including magnetic resonance angiography and MRV is recommended. In a study (n = 97) by Rozen (66), the majority (87%) of patients with primary NDPH had normal MRI studies, while the rest had white matter abnormalities. None in this cohort had infarct-like lesions. Among the patients with NDPH with white matter abnormalities, all of them had co-existing cardiovascular risk factors (66). CSF studies should be considered to exclude a derangement in intracranial pressure, infection, or disseminated neoplasm if clinically warranted. Systemic infection and inflammation should also be carefully ruled out.

Treatment of new daily persistent headache

NDPH is often treated with various abortive (i.e. non-steroid anti-inflammatory drugs, acetaminophen, or triptans) and preventative medications (i.e. tricyclic antidepressants, beta blockers, flunarizine, serotonin–norepinephrine reuptake inhibitors, certain antiepileptic drugs (including valproic acid), topiramate, etc.) commonly used in migraine or TTH. However, there have been no double-blind randomized controlled trials to evaluate their efficacy. In one Japanese report, all patients (n = 30) were treated with muscle relaxants and 28 of them also received other medication concomitantly. Only eight of 30 responded to the muscle relaxants-based therapy (7). In one US series (n = 71), NDPH with TTH features were more likely to have pain reduction after greater occipital, lesser occipital, auriculotemporal, supraorbital, or supratrochlear nerve blocks, but this did not reach statistical significance (9). A Taiwanese series (n = 92) reported that patients with early treatment (3–6 months after NDPH onset) were more likely to have a better response at follow-up; however, no single medication seemed superior (10). In smaller series, responses to haloperidol (67), dihydroergotamine (68), and greater occipital nerve block were reported (69). In another report, nine patients with recent extracranial infection several weeks prior to the onset of NDPH-like headaches were treated with intravenous methylprednisolone pulse therapy (1 g daily for 5 days). All of the nine patients had nearly complete improvement by week 8 (70). However, only four of nine had a disease duration of more than 3 months and met the current criteria for NDPH (11). In the paediatric population, the more commonly prescribed medications were amitriptyline, topiramate, valproic acid, and gabapentin, but the responses were variable (17).

In general, NDPH is treated similarly to CM and CTTH, and the acute and prophylactic treatments of those disorders are extrapolated for use in NDPH according to the headache phenotype (migrainous or tension-type). Although there is no consensus for optimal therapy, NDPH is commonly associated with medication overuse headache (MOH) in adult patients (34.8–75%) (9,10,14,19) and less commonly in paediatric patients (8.7%) (8). It is reasonable to treat NDPH associated with MOH with withdrawal therapy, either abrupt discontinuation or tapered withdrawal (71). Of note, the diagnosis of NDPH must be established before a subsequent diagnosis of MOH.

Prognosis of new daily persistent headache

NDPH is generally considered very difficult to treat and the headache usually persists despite various therapeutic interventions. There might be at least two subtypes of NDPH considering the disease courses: one type that remits within a certain period, usually within 24 months, with or without further relapse (remitting NDPH); the other type lasts for years and is rather resistant to therapies (persistent NDPH). In the initial report by Vanast (1), presumably, most of the patients fell into the remitting NDPH category, as 86% of the male patients and 73% of the female patients became headache-free by 24 months. In the Japanese report, eight of 30 patients had very good responses to treatment, including two patients who became headache-free. However, the remaining six responders still had daily headache, despite some improvement in the quality of life. Thus, 28 of 30 still had severe or daily headache (7). In the American series (n = 71), 54 (76.1%) had persistent headache, 11 (15.5%) had remission in a median duration of 21 months, and six (8.5%) had relapsing–remitting NDPH (9). In the Taiwanese series, among those successfully followed patients (n = 87), 57 (66%) had a good outcome (>50% reduction in frequency) including 23 (26.4%) headache-free after an average of 2 years of follow-up. Of note, in this study, 56 (60.9%) had a headache duration between 3 and 6 months before the first clinical visit, and these patients were more likely (hazard ratio 2.71) to be headache-free than those with a disease duration > 6 months (10). In an Indian study (n = 63), two-thirds of the patients had at least > 50% reduction in headache frequency (23). Another US study followed 28 of 51 paediatric patients with NDPH and 20 of these still had headache, but only eight had chronic daily headache (18). Owing to the discrepancy in the enrolment criteria among studies, interstudy comparisons are difficult. However, the headache remission in certain patients, including those with shorter disease durations, may reflect the fact that NDPH is a heterogeneous syndrome of different aetiologies. For example, patients with secondary NDPH to infection might get better after the infection is successfully treated. Moreover, certain patients with 'primary NDPH' may indeed reach remission within a certain period, but, to date, there is no good predictor for the remitting NDPH subtype.

Conclusion

NDPH is a heterogeneous syndrome with different aetiologies. The update in the diagnostic criteria set forth in ICHD-3 reflects the diverse clinical symptomatology and that migraine features should also be incorporated. Still, in order to make a diagnosis, the physician must scrutinize each case for any possible alternative diagnoses before making the diagnosis of NDPH. The current treatment of

NDPH is not satisfactory. More studies are needed to provide better understanding and hopefully better treatment in the future.

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31

Chronic migraine and medication overuse headache

David W. Dodick and Stephen D. Silberstein

Introduction

Chronic migraine (CM) is a subtype of migraine characterized by headache that occurs on ≥ 15 days per month for ≥ 3 months. The estimated global prevalence of CM varies from 1% to 3%, depending on the population, ethnicity, case definition, and case ascertainment methodology (1–7). Persons with CM experience significantly more functional impairment and reduced quality of life compared with those with episodic migraine (EM) (6–8).

The case definition for CM has evolved over the past three decades. The observation that headache frequency can increase over time in some individuals with migraine is centuries old. However, in 1987, Mathew introduced the term *transformed migraine* (TM) to characterize a group of patients with migraine whose headache frequency and character gradually increased, or *transformed*, over time in a pattern or daily or near-daily headache (9). Among this group, most had migraine without aura and the majority overused acute headache medications. The discontinuation of the overused medication(s) often resulted in clinical improvement. Saper et al. (10) made similar observations, noting that the vast majority of patients in clinical practice with chronic headache (> 15 days/month) had a history of EM, overused acute medication, and improved and cessation of overuse.

Silberstein and Lipton, and colleagues (11), developed operational diagnostic criteria for TM that required a history of International Classification of Headache Disorders (ICHD)-1-defined migraine, headache on at least 15 days per month lasting > 4 hours per day on average, a history of transformation, and subtypes based on the presence or absence of acute medication overuse (**Box 31.1**). These criteria were revised in 1996 to include either a history of escalation over 3 months, a history of EM, or a headache at some time that meets ICHD criteria for migraine other than duration, as a remote history of transformation could not be recalled by up to 40% of patients (**Box 31.2**) (11). No causal role of acute medication overuse was assigned and a hierarchical diagnostic rule was established to avoid a concurrent diagnosis of chronic tension-type headache (TTH) for those who met TM criteria. Prior to the development of operational diagnostic criteria by the ICHD, these criteria had been used in clinic- and population-based studies, as well as in clinical trials around the world (12–14).

CM was added as a complication of migraine for the first time in the ICHD-2 in 2004 (Table 31.1) (15). However, when acute medication overuse was present, the diagnosis of CM could not be applied concurrently. Instead, individuals could receive diagnoses of the preceding migraine subtype, probable CM, and probable medication overuse headache (MOH). A diagnosis of CM would only be applied if the criteria for CM were still met 2 months after the discontinuation of overuse. Not only were these criteria cumbersome to apply in clinical practice, but they did not allow for the existence of MOH in the absence of chronic headache (i.e. headache < 15 days per month but overuse of medication). Moreover, the results of field studies of ICHD-2 CM criteria revealed that the majority of individuals who meet TM criteria do not meet CM criteria, and patients meeting the ICHD-2 diagnostic criteria for CM are rare in clinical practice (16,17).

Based on these shortcomings, the Classification Committee of the International Headache Society published a revised version of the criteria for CM in 2006 (Table 31.1) (18). The ICHD-2R criteria required that patients have > 15 headache days per month for at least 3 months, with ≥ 8 migraine days (or ≥ 8 days on which headaches were treated and relieved by a triptan or an ergot). The ICHD-2R criteria have been field-tested and validated in clinical practice (17,19). The ICHD-2R criteria have also been validated on the basis of data obtained through the pivotal phase III studies of onabotulinum toxin A for the treatment of CM (20–22). The ICHD-2R criteria were therefore included in the third edition of the ICHD (ICHD-3 Beta (ICHD-3B)) (23). ICHD-3B no longer considered CM a complication of migraine, allows both migraine with and without aura, excludes the diagnosis of TTH, and allows the concurrent diagnosis of CM and MOH ('1.3 Chronic migraine' and '8.2 Medication overuse headache') (**Table 31.1**). ICHD-3B enabled a period of time for field-testing and incorporation into the World Health Organization's 11th edition of the International Classification of Diseases (ICD-11) prior to the final published version of ICHD-3 in 2018 (see also Chapter 1).

Despite the advance, ICHD-3B criteria remained challenging to implement in clinical practice (24). The ability to recall the response

Box 31.1 Original proposed criteria for transformed migraine

1.8 Transformed migraine (TM)
- **A** History of episodic migraine meeting any IHS criteria 1.1–1.6.
- **B** Daily or almost daily (> 15 days/month) head pain for > 1 month.
- **C** Average headache duration of 4 hours/day (if untreated).
- **D** History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months.
- **E** At least one of the following:
  1. There is no suggestion of one of the disorders listed in groups 5–11
  2. Such a disorder is suggested, but it is ruled out by appropriate investigations
  3. Such disorder is present, but first migraine attacks do not occur in close temporal relation to the disorder.

1.8.1 Transformed migraine with medication overuse.

1.8.2 Transformed migraine without medication overuse.

IHS, International Headache Society.

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to migraine-specific medication is often not possible. This criterion also assumes that response to 'migraine-specific' medication implies the attack is a migraine, but other primary headache disorders and even secondary headaches may respond to triptans. Furthermore, the term 'relieved' by triptan or ergot is not operationally defined. This approach also makes diagnosis more difficult in those patients for whom triptans and ergots are contraindicated or not available. Furthermore, an accurate diagnosis would require very detailed headache diaries with all pain and associated symptoms recorded, rarely available at the time of an initial evaluation. Silberstein, Lipton, and Dodick have recommended, based on the evidence available and extensive field-testing already performed, that the ICHD-3B criteria for CM be modified by removing the criterion that specifies that CM must occur in a patient with at least five prior migraine attacks, adding probable migraine to C1 and C2, removing the criterion (C3) that treatment and relief of headache by a triptan or ergot, adding the criterion that the headache does not meet criteria for new daily persistent headache or hemicrania continua, and defining subtypes based on the continuous or remitting nature of the pain (**Box 31.3**) (24). These revisions to the ICHD-3 criteria for CM (see Chapter 1) will facilitate large-scale international epidemiological, genetic, and treatment studies on each subtype, while maintaining the clinical and biological homogeneity of this patient population.

Box 31.2 Silberstein–Lipton (revised) criteria for chronic migraine

1.8 Chronic migraine
- **A** Daily or almost daily (> 15 days/month) head pain for > 1 month.
- **B** Average headache duration of > 4 hours/day (if untreated).
- **C** At least one of the following:
  1. History of episodic migraine meeting any IHS criteria 1.1–1.6
  2. History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months
  3. Headache at some time meets IHS criteria for migraine 1.1 to 1.6 other than duration.
- **D** Does not meet criteria for new daily persistent headache (4.7) or hemicrania continua (4.8).
- **E** At least one of the following:
  1. There is no suggestion of one of the disorders listed in groups 5–11
  2. Such a disorder is suggested, but it is ruled out by appropriate investigations
  3. Such a disorder is present, but first migraine attacks do not occur in close temporal relation to the disorder.

IHS, International Headache Society.

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In addition to the overuse of acute headache medications, there are several other modifiable risk factors that are associated with progression from EM to CM, including high baseline attack frequency (one per week), caffeine consumption, snoring, female sex, obesity, and the inadequate acute treatment of migraine attacks (25–29). Female sex, allodynia, asthmatic bronchitis, head injury, low socioeconomic status, depression, anxiety, and comorbid pain disorders are also risk factors for CM. The recognition and modification of these risk factors is important in clinical practice. Compared to EM, individuals with CM experience substantially reduced health-related quality of life and significantly higher impact on daily activities, direct medical costs, and rates of medical comorbidities (6–8,30). CM is also associated with greater rates of healthcare resource utilization, including more frequent visits to primary care physicians, specialists, and emergency departments. Individuals with CM are also more frequently hospitalized and undergo more diagnostic tests.

Despite the availability of evidence-based guidelines intended to inform clinical decision-making and the care of patients with migraine, the management of migraineat a population level remains suboptimal. Obstacles to optimal migraine management include female sex, lack of health insurance, failure to present for medical attention, failure to receive an accurate diagnosis, and failure to receive a minimally appropriate treatment regimen. Among those with CM, only 41% currently consult a healthcare provider and only 25% receive an accurate diagnosis (31). Even among those who receive an accurate diagnosis, over half are not prescribed an acute and preventive treatment. The use of screening tools such as the Identify (ID)-Migraine and ID-Chronic Migraine (ID-CM) (32,33), and the implementation of evidence-based guidelines for the acute and preventive treatment of migraine, should enhance the likelihood of patients receiving an accurate diagnosis and optimal treatment (34–41).

Medication overuse headache

MOH is a prevalent condition. Epidemiological studies have demonstrated that 1–2% of the general population is affected (42–45). However, as a causal mechanism is seldom obvious and the diagnosis is made simply on the basis of the arbitrary number of days an acute medication is used over the course of 3 months, the true prevalence remains unknown. In other words, medication overuse in epidemiological studies is a surrogate for a diagnosis of MOH. In addition, most studies reporting CM prevalence did not specifically address whether MOH or medication overuse was also present. Natoli et al. (1) found that among adults with CM, the prevalence of medication

Table 31.1 Diagnostic criteria for transformed migraine (TM) according to Silberstein–Lipton criteria and for chronic migraine (CM) according to ICHD-2R and ICHD-3B (see also Chapter 1)

Silberstein-Lipton TM	ICHD-2R CM	ICHD-3 B
A Daily or almost daily (> 15 days a month) head pain for > 1 month **B** Average headache duration of > 4 hours (if untreated) **C** At least one of the following: 1 History of episodic migraine meeting any IHS criterion 1.1–1.6 2 History of increasing headache frequency with decreasing severity of migrainous features over at least 3 months 3 Headache at some time meets IHS criteria for migraine 1.1–1.6 other than duration **D** Does not meet criteria for new daily persistent headache (4.7) or hemicrania continua (4.8)	**A** Headache on ≥ 15 days/month for 3 months **B** Occurring in a patient who has had at least five attacks fulfilling criteria for '1.1 Migraine without aura' **C** On ≥ 8 days per month, for at least 3 months, headache fulfils criteria for migraine C1 and/or C2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura 1 Criteria C and D for '1.1 Migraine without aura' 2 Treated or relieved with triptans or ergotamine before the expected development of C1 above **D** No medication overuse and not attributable to other causative disorder	**A** Headache on ≥ 15 days per month for at least 3 months **B** Occurring in a patient who has had at least five attacks fulfilling criteria for '1.1 Migraine without aura' and/or '1.2 migraine with aura' **C** On ≥ 8 days per month for at least 3 months one or more of the following criteria were fulfilled 1 Criteria C and D for '1.1 Migraine without aura' 2 Criteria B and C for '1.2 Migraine with aura' 3 Headache considered by patient to be onset migraine and relieved by a triptan or an ergotamine derivative **D** Not better accounted for by another ICHD-3 diagnosis

ICHD, International Classification of Headache Disorders; IHS, International Headache Society.

Source data from: *Neurology*, 47, 4, Silberstein SD., Lipton RB, and Sliwinski M, Classification of daily and near-daily headaches: field trial of revised IHS criteria, pp. 871–5, 1996; *Cephalalgia*, 26, 6, Headache Classification Committee, Olesen J, Bousser MG et al., New appendix criteria open for a broader concept of chronic migraine, pp. 742–6, 2006; *Cephalalgia*, 33(9), The International Classification of Headache Disorders, 3rd edition (beta version), pp. 629–808. doi: 10.1177/0333102413485658. International Headache Society 2013.

overuse was 31–69%. In clinical populations, the prevalence also varies widely depending on the population. In European headache centres, 4–10% of patients have MOH, while in US specialty headache clinics, as many as 80% of patients who present with chronic headache use analgesics on a daily or near-daily basis (46–48).

The overuse of acute headache and pain medications is common among individuals with migraine who experience frequent attacks and poses a unique treatment challenge for clinicians. The threshold number of days that defines medication overuse depends on the medication (> 10 days per month for opioids, butalbital-containing medications, triptans, ergots, combination analgesics; > 15 days for simple analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs)) (**Box 31.4**). The greatest risk of progressing from EM to CM is associated with opioids (odds ratio (OR) 1.4) and butalbital-containing medications (OR 1.7), and can occur with as few as five dosages per month (8,25). Individuals with CM and medication overuse have even poorer quality of life, greater disability, and greater losses in productivity than people who have CM without medication overuse (8).

Box 31.3 ICHD-3 revised chronic migraine criteria

A Headache (migraine- like or tension- type- like) on ≥15 days/ month for >3 months, and fulfilling criteria B and C.

B Occurring in a patient who has had at least five attacks fulfilling criteria B-D for 1.1 *Migraine without aura* and/ or criteria B and C for 1.2 *Migraine with aura*.

C On ≥8 days/ month for >3 months, fulfilling any of the following:
1 Criteria C and D for 1.1 *Migraine without aura*.
2 Criteria B and C for 1.2 *Migraine with aura*.
3 Believed by the patient to be migraine at onset and relieved by a triptan or ergot derivative.

D Not better accounted for by another ICHD- 3 diagnosis.

(See also Box 1.2).

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Diagnostic criteria for MOH were introduced in 2004 (15). However, the first ICHD-2 classification of MOH stated that a diagnosis of headache attributed to a substance becomes definite only when the headache resolves or greatly improves after the substance is discontinued for a period of 2 months. If improvement did not then occur within the 2-month period, the MOH diagnosis was discarded. Therefore, MOH could only be diagnosed after it resolved. Moreover, it excluded the possibility that medication-induced headache may not resolve even after discontinuation. This criterion was therefore eliminated in ICHD-2R and, as noted earlier, a concurrent diagnosis of MOH and CM could be assigned according to ICHD-3B.

MOH is currently defined as headache occurring on ≥ 15 days per month together with the regular overuse, over a period of 3 months, of acute headache medication on ≥ 10, or ≥ 15 days per month, depending on the medication (23). The clinical features of CM and MOH appear to be very similar. In the Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy (PREEMPT) studies, patients kept daily diaries for almost 1 year. In this sample, patients with CM with or without overuse had a disease duration of approximately 20 years and an average of 20 headache days per month (21). While the previous literature suggested that most headache days assume the phenotype of TTH as migraine becomes more chronic or becomes associated with medication overuse, the PREEMPT studies demonstrated that the majority (n = 19/20) of the days with headache met the diagnostic criteria for migraine or probable migraine.

Box 31.4 ICDH-3 criteria for medication overuse headache

A Headache occurring on ≥ 15 days/month in a patient with a pre-existing headache disorder.

B Regular overuse for > 3 months of one or more drugs that can be taken for acute and/or symptomatic treatment of headache.

C Not better accounted for by another ICHD-3 diagnosis.

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Pathophysiology of chronic migraine and medication overuse headache

The pathophysiology of CM is not completely understood. Central sensitization of trigeminal sensory pain pathways is thought to play a major role in the development of CM (49,50). Cutaneous allodynia, the clinical manifestation of central sensitization, is present in most individuals during migraine attacks and between attacks in those with frequent migraine (49,51–53). Cutaneous allodynia has been shown to be a risk factor for migraine progression in population-based studies (49,51–53). Severity of allodynia has been shown to be greater in individuals with CM than in those with EM (54). In addition, higher rates of persistent allodynia between attacks have been demonstrated in those with CM (with or without acute medication overuse) versus EM, indicating the possibility of a progressive lowering of pain thresholds as a contributing factor in those with CM (55). Lower pain thresholds in patients with CM (56) and atypical cortical processing of cutaneous nociceptive input (57,58), support the hypothesis of disrupted central pain mechanisms as a pathophysiological process involved in the development of CM. In addition to functional changes in cortical sensory processing in patients with CM, imaging evidence of structural brain changes, including cortical thinning and regional brain volumes, has also been correlated with changes in pain thresholds and shown to distinguish CM from EM (53,59).

Central sensitization might occur during repeated migraine attacks through impaired descending inhibition and/or enhanced descending facilitation of nociception. Functional imaging studies have demonstrated abnormal brainstem activation in EM and CM, suggesting that dysfunction of descending inhibitory pathways might facilitate migraine attacks. Functional imaging studies have also demonstrated interictal hypofunction of lateral descending pain modulatory circuits in patients with migraine (60). The role of descending pain modulatory circuits in CM was reinforced by a recent study (61), which demonstrated increased hypothalamic activation in response to painful trigeminal stimulation in CM compared to patients with EM and non-headache controls. In addition, the anterior hypothalamus was found to be associated with the initiation of attacks in CM, while the posterior hypothalamus appears to be linked to the acute painful phase of the individual attack. The anterior hypothalamus has also been shown to be involved in the premonitory phase of migraine attacks and has long been implicated in the pathogenesis of migraine and other primary headache disorders. The hypothalamus is a part of the descending pain modulating network (62), and the increased activation patterns observed in CM may indicate a reduced threshold for the initiation of attacks in CM, which, in combination with other risk factors as described earlier, might lead to an enhanced susceptibility to frequent attacks.

Electrophysiological studies have also demonstrated functional changes that characterize the brain of those with CM versus EM. Persistent enhanced cortical excitability, exceeding that in patients with EM or in migraine-free controls, has also been demonstrated in individuals with CM (63–67). These findings suggest central inhibitory dysfunction, increased cortical hyperexcitability, or both, in the development of CM.

Overuse of acute headache medications is a major risk factor for the development of CM, and recent studies have suggested potential underlying mechanisms. Animal models have revealed persistent pronociceptive adaptations following exposure to opioids and triptans, resulting in enhanced sensitivity to stimuli that trigger migraine in humans (68,69). In this model, the sustained or repeated administration of triptans to rats elicited cutaneous tactile allodynia and increased labelling for calcitonin gene-related peptide (CGRP) in trigeminal dural afferents that persisted long after discontinuation of triptan exposure. Even weeks after drug exposure and sensory thresholds returned to baseline, enhanced cutaneous allodynia and increased blood levels of CGRP occurred after challenge with a typical migraine trigger—nitric oxide. In a separate set of experiments using a similar animal model, prolonged sumatriptan exposure significantly decreased electrical stimulation threshold to generate cortical spreading depression (CSD) (70). In addition, CSD and environmental stress increased expression of early gene products (c-Fos) in the trigeminal nucleus caudalis, and these effects were blocked by topiramate. These experiments demonstrated that overuse of acute headache pain medications induces neural adaptations that result in a state of latent sensitization, and lower CSD threshold, both of which lead to increased trigeminal activation, and may represent potential biological mechanisms of CM related to overuse of acute headache medications.

Treatment

The management of CM, especially when associated with medication overuse, can be challenging (see also Chapter 32). There is debate concerning whether patients should undergo discontinuation of the overused medication alone or with the addition of preventive treatment, or, whether withdrawal is necessary if preventive medication is started. The European Federation of Neurological Sciences guideline recommends the abrupt discontinuation or taper of the overused medication and that preventive drug treatment be started before or simultaneously with discontinuation (46). However, to avoid exposure to other medications and the potential risk, some recommend discontinuation of overused medications and careful follow-up in 2–3 months to determine the need for preventive medication (71).

A recent systematic review evaluated the evidence to support discontinuation alone, discontinuation plus preventive therapy, or preventive therapy without discontinuation (72). Unfortunately, early discontinuation alone studies usually allowed preventive treatment before or after discontinuation. For example, in one study involving 337 patients with probable MOH who underwent discontinuation of overused medications, a significant (46%; $P < 0.0001$) decrease in headache frequency occurred. However, only 64% of the patients completed the 2-month study and of those who did complete the study, 45% improved, 48% had no changes, and 7% experienced an increase in headache frequency (73). Patients with migraine had a significantly larger reduction in headache frequency than patients with TTH (67% and 0%; $P < 0.001$) or patients with both migraine and TTH (37%; $P < 0.01$). Triptan or ergot overusers improved the most ($P < 0.0001$). Two other prospective studies evaluated the effect of intensive advice to discontinue the overused medication (74,75). Antiemetics and simple analgesics were allowed for rescue therapy, but preventive medication was not allowed. Both studies showed high discontinuation rates (79% and 76%, respectively), as well as

significant reductions (60–70%) in headache days and days with acute medication use. However, in one study the effect was more prominent in patients with simple MOH than in those with complicated MOH (patients with medical or psychiatric comorbidity, psychosocial problems, and history of relapse). The discontinuation rate was 92.1% of 51 patients with simple MOH and 65.3% of 49 patients with complicated MOH ($P < 0.01$).

Studies that combined discontinuation with the addition of preventive medication also vary widely with regard to study setting (inpatient vs outpatient), the rescue medications allowed, and the type of preventive medications used. However, several studies report significant improvements in quality of life and reductions from baseline in headache days, acute medication consumption, headache-related disability, and depression and anxiety within 1 year after discontinuation combined with preventive medication (76). A recent international study involving headache centres from Europe and Latin America (COMOESTAS project (Continuous Monitoring of Medication Overuse Headache in Europe and Latin America: development and STAndardization of an Alert and decision support System)) established a protocol for the management of MOH (77). Patients were included for either inpatient or outpatient early discontinuation. Preventive treatment was started simultaneous with discontinuation and the selection of therapy was made on the basis of the primary headache and comorbid conditions that were present. At the end of the study period, approximately two-thirds of the enrolled patients ($n = 376$) were no longer overusing acute medications, nearly half had remitted to an episodic pattern of headache, and there was a notable reduction in disability and in the number of patients with depression and anxiety (78). The limitations of the COMOESTAS project were the exclusion of patients who had failed attempts at discontinuation in the past, who were using preventive medications, or who had significant psychiatric illness.

There are several trials that suggest that the use of preventive medication without withdrawal of overused medication(s) may be an effective strategy. Hagen et al. (79) randomized 56 patients to receive preventive treatment without withdrawal, a standard outpatient withdrawal programme without preventive treatment, or no specific treatment (79). The change in monthly headache days did not differ significantly between groups. However, the group started on prevention without withdrawal had the highest decrease in headache days compared with baseline, and a significantly greater reduction in total headache index ((headache days/month × headache intensity × headache hours)) at 3 ($P = 0.003$) and 12 ($P = 0.017$) months compared with the group who underwent withdrawal without prevention. After 1 year, 53% of patients in the prevention group were responders (> 50% decrease in monthly headache days) versus 25% in the withdrawal group ($P = 0.081$). The responder rate was also significantly higher for the prevention group than controls (41% vs 5%; $P < 0.01$). This is the first randomized study, despite the small sample size, that evaluated the efficacy of early introduction of preventive medication compared with abrupt discontinuation therapy and a control group. This strategy was an effective method to reduce headache days and headache burden and the improvement was sustained after 4 years of follow-up (80).

Onabotulinum toxin A was also evaluated as a preventive treatment for CM in patients with and without medication overuse. In two phase III, 24-week, double-blind, parallel-group, placebo-controlled studies involving 66 global sites, 1384 patients received either onabotulinum toxin A (155–195 units) or placebo. Medication overuse was present in 65.3% ($n = 904$) of the participants (21,22,81). In the CM with medication overuse subgroup, a planned secondary analysis revealed a significant reduction in the group receiving onabotulinum toxin A for the primary end point of headache days (8.2 vs 6.2; $P < 0.001$). Significant reductions were also demonstrated in migraine days ($P < 0.001$), moderate/severe headache days ($P < 0.001$), cumulative headache hours on headache days ($P < 0.001$), headache episodes ($P = 0.028$), migraine episodes ($P = 0.018$), and the percentage of patients with severe headache-related disability ($P < 0.001$). However, while there was an overall reduction in consumption of acute medications in both groups, there was no significant difference between the groups. This indicated that the difference between the treatment groups could not be accounted for by the reduction or discontinuation in acute medication consumption. The limitations of this study was that it was not a pure MOH population and the analysis was secondary and in a subgroup.

The efficacy of onabotulinum toxin A 100 units as a preventive treatment plus discontinuation of medication overuse was evaluated in a placebo-controlled study involving 68 patients (82). There was no difference in the reduction of headache days or headache-related disability between the two groups, but there was a significant reduction in the acute medication consumption at 12 weeks in the active treatment group (secondary analysis). This study supports the use of onabotulinum toxin A along with early discontinuation in CM with medication overuse. The smaller sample size, lower dosage, shorter follow-up period, fewer injections, and fewer injection sites in this study may account for the differences compared to the PREEMPT studies.

Diener et al. (83,84) reviewed the results from two similarly designed, randomized, placebo-controlled, multicentre studies of CM that were conducted in the USA and the European Union (EU) of the efficacy and safety of topiramate for the treatment of CM in patient populations both with and without medication overuse. Topiramate was effective for the treatment of patients with CM. The intention-to-treat (ITT) population in the US study consisted of 306 participants (topiramate, $n = 153$; placebo, $n = 153$); the ITT population in the EU study consisted of 59 participants (topiramate, $n = 32$; placebo, $n = 27$) (80). A post-hoc analysis in the subset of patients with medication overuse in the US trial trended towards significance but did not reach a statistical difference between topiramate and placebo in the reduction in migraine/migrainous days ($P = 0.059$). In the EU trial, topiramate-treated patients with medication overuse experienced a significant reduction in the mean number of migraine days versus placebo treatment ($P = 0.03$). There were several key differences between the patient populations. In the US trial, 115 of 306 (37.6%) patients versus 46 of 59 (78.0%) patients in the EU trial reported using acute medications for migraine that met the definitions of medication overuse during the 28-day prospective baseline period. In the US, the most commonly overused medications were triptans and analgesics; 40% of patients overused NSAIDs and 6% overused opioids. In the EU trial, the vast majority of overused medications were triptans. Butalbital-containing analgesics were allowed in the US trial, but no butalbital-containing analgesics were available or prescribed in the EU trial.

The efficacy of nabilone, a synthetic cannabinoid CB_1 receptor agonist, was evaluated in a 30-patient, randomized, double-blind, active-controlled (ibuprofen 400 mg), crossover study for the

treatment of MOH (85). Nabilone 0.5 mg daily significantly reduced daily acute medication consumption and headache intensity at 20 weeks compared with ibuprofen. In a comparator study of prevention without discontinuation, both pregabalin 150 mg daily and topiramate 100 mg daily significantly improved disability while decreasing monthly headache frequency and days of acute medication use (86). There were no significant between-group differences between the two drugs in this 16-week study.

Non-pharmacological treatment

Occipital nerve stimulation (ONS) has been evaluated for the treatment of CM with and without medication overuse. In a study of 34 patients with CM, of whom 85% had medication overuse, ONS was reported to significantly decrease headache frequency, intensity, and NSAID use from baseline after acute medications were discontinued 2 months previously (87). In another ONS study, patients with medication overuse had significantly less pain relief than those without medication overuse (mean 28% vs 78%; $P = 0.0498$) (88).

In a study designed to investigate the efficacy of acupuncture compared with topiramate treatment for the prevention of CM, 66 patients were randomly assigned to acupuncture administered in 24 sessions over 12 weeks or topiramate 100 mg daily (89). A significantly larger decrease in the mean monthly number of moderate/severe headache days (primary end point) was observed in the acupuncture group compared the topiramate group ($P < 0.01$) Significant differences favouring acupuncture were also observed for all secondary efficacy variables. Similar results were seen in the group with medication overuse. Adverse events occurred in 6% of the acupuncture group and 66% of the topiramate group

Emerging therapy

The important role of CGRP in the pathogenesis of EM and CM has led to the development of evaluation of monoclonal antibodies (mAbs) targeting GCRP and its receptor. Three mAbs targeting CGRP (fremanezumab, eptinezumab, galcanezumab) or its receptor (erenumab) have now been shown in phase II trials to be well tolerated and effective in the prevention of EM and CM (fremanezumab, erenumab) (90–95). Erenumab, galcanezumab, and fremanezumab have also recently reported positive results in phase III placebo-controlled trials in EM and CM, but these results await final publication. Thus far, the side effect profile appears very limited and there are as yet no serious safety concerns that have arisen in preliminary and pivotal trials. However, their safety in situations when the blood–brain barrier is compromised or on a developing fetus is still uncertain and long-term extension studies and postmarketing data will be needed to determine their overall safety profile.

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32

Frequent headaches with and without acute medication overuse

Management and international differences

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Introduction

In headache parlance, frequent headaches are those that occur on at least 15 days per month, for more than 3 months, and are grouped under the umbrella term 'chronic daily headache' (CDH). Although this is not an official International Headache Society (IHS) term, it was used for many years and it clearly suggests the types of headache that go on for years and occur on most days of the month. These include the following headaches from various sections of the International Classification of Headache Disorders (ICHD)-3 classification (1): chronic migraine (CM); chronic tension-type headache (CTTH); hemicrania continua (HC); new daily persistent headache (NDPH); chronic cluster headache (CCH); nummular headache; and medication-overuse headache (MOH) (see also Chapter 31). For migraine and tension-type headache, the word chronic denotes 15 or more headaches per month, not how long it is has lasted. For secondary headaches, chronic refers to duration, usually denoting more than 3 months.

CDH is a significant problem worldwide. In a study performed as part of the initiative, 'Lifting the Burden: the Global Campaign to Reduce the Burden of Headache Worldwide', the global prevalence of CDH was found to be 3.4%. Although the data on CDH, as compared to migraine or tension-type headache (TTH), is relatively sparse, CDH seems to be most common in Central/South America (5%) and least common in Africa (1.7%) (2).

A summary of the approaches to CM, MOH, and CCH treatment is presented in this chapter, with an emphasis on international differences noted in the medical literature. In addition, we have asked a number of prominent headache specialists around the world to discuss their own management strategies for these disorders. Their comments are presented in the Appendices 32.1–32.3.

HC, now included in the trigeminal autonomic cephalgias (TAC) section of the ICHD-3 (1), is not discussed in detail as indomethacin is considered the standard of treatment. Likewise, CTTH is widely treated with non-steroidal anti-inflammatory drugs (NSAIDs) for acute treatment and with tricyclic antidepressants for preventive treatment (3–5), and NDPH is generally treated empirically as there have been no randomized, placebo-controlled trials of acute or preventive medications. These headache disorders are reviewed elsewhere in this textbook.

Considerations in international comparisons of headache treatment

Differences in healthcare systems

When evaluating international differences in headache treatment, a major consideration is the differences in healthcare systems between countries. The cost of care and the major cost drivers vary widely, thus affecting the differences in available headache therapies, delivery of care, access to medications and specialist consultations, and cost of services (6). The following is a snapshot of several healthcare systems around the world, and how those systems affect the delivery of headache care.

In Germany, a government-created reimbursement system for 'integrated care' of chronic diseases exists (7), which involves a multidisciplinary approach and care across the sectors of the healthcare system, integrating specialist clinics at large hospitals and physicians in private practice. This has allowed for the creation of integrated headache centres staffed by neurologists, behavioural psychologists, physical and sports therapists, headache nurses, and consultants from psychosomatic medicine, psychiatry, and dentistry. In addition, the databases of insurance companies can be accessed, such that patients with chronic headache, medication overuse, or risk factors for the development of chronic headaches can be identified and invited for evaluation at the headache centre without a referral or co-payment. Another important aspect of this system is the higher reimbursement rates for these headache centres and participating private neurologists. In addition to improved patient outcomes, integrated headache care is cost-effective, with an average yearly cost savings of 30%, attributed to decreased

diagnostic testing, as well as reduced hospital admissions and visits to emergency departments (7).

In contrast to the European model of integrated headache care, which also encompasses collaboration between the government, insurance companies, and headache centres, headache care in the USA is 'fragmented' and somewhat dysfunctional (7). Patients are at the mercy of their private physician's interest in and knowledge of headache for their care, and many insurance systems discourage referrals to neurologists and to the limited number of available headache specialists. If a patient has no insurance or an inadequate policy, headache care can be difficult to access and inadequate. There are very few academic headache centres, most of which suffer from financial difficulties. Headache education in medical school and neurology training is limited, and headache sections are rare in academic neurology departments. Of these headache centres, very few have an inpatient programme for complicated patients. Furthermore, unlike in European countries such as Germany and Denmark, there is no increased reimbursement or compensation for complicated patients, and no funding for multidisciplinary care.

In Brazil, headache treatment by specialists is offered in either of two ways. One is delivered by public services from public hospitals and is directed towards non-paying patients. The other is through private centres and centres of excellence, which are usually situated in the very few high-standard university hospitals (not available in Rio de Janeiro) and are directed to paying patients. The public system delivers a traditional, non-comprehensive approach, in which monotherapy is usually prescribed. The private centres offer a multidisciplinary approach and frequently use a combination of drugs and the latest techniques.

In some of the best headache centres in Brazil, patients are often evaluated in long-duration initial consultations and undergo psychological screening. Most have refractory or intractable headaches and/or present with various comorbidities. They have seen multiple previous physicians and have not usually had adequate care for their level of headache or other medical issues.

Canada comprises 10 provinces and three territories, each of which has a separate healthcare system with different aspects covered by each plan. In addition, there are private plans that supplement the costs of medications and certain forms of treatment. However, the training of doctors is fairly standard in each province, so the level of expertise should be fairly consistent. Doctor fees and the cost of laboratory testing and radiology are covered by Provincial Health plans. While most headache care in Canada is based on individual physician–patient encounters, there are a number of headache clinics, such as the one in Women's College Hospital in Toronto, the John Kreeft Migraine Clinic in London, and two in Montreal. Headache patients are also seen in pain clinics, which are generally run by anaesthetists or general practitioners with a special interest in pain and headache.

In Australia, health care is provided through a mix of public and private sector providers. The Therapeutic Goods Administration, Australia's regulatory authority for medications, approves drugs for various indications, while a separate committee determines which medications will be subsidized by the government through the Pharmaceutical Benefits Scheme. Specialist headache care is usually provided through neurologists with an interest in headache as there are very few headache centres or clinics in the country.

Taiwan has a government-run, single-payer healthcare system with a low co-payment for outpatient and inpatient services. Over 99% of the population is covered by national health insurance. Physician referrals are not required for specialist care, unlike in the US, UK, or Canada, and patients are therefore able to access tertiary care institutions for primary care (8). As headache is an emerging subspecialty in Taiwan, headache specialists are rare (8).

Regional and cultural factors

Regional factors also play an important role when considering international differences in headache treatment. In mainland China, until a few years ago there were no headache centres and most patients did not get much care in their local clinics. Today, China has many headache centres that have been developed along with guidelines set up in conjunction with the IHS. In low- and middle-income (LAMI) countries, life-threatening conditions are more prevalent than in higher-income countries, and headache care is thus relegated to a lower priority. In these regions, a large percentage of the population resides in rural areas and rates of illiteracy are high, further precluding access to medical care. In addition, headache research in LAMI countries in the developing world is limited, for a number of reasons, including lack of resources, lack of access to medical information and published literature, technical difficulties in performing studies in rural areas, and language barriers. As research done at the local level helps to raise awareness, shape policy, and encourage the development of services, the paucity of research and publications impacts on the availability of headache treatment in these areas (9).

Cultural factors may affect the experience and perception of pain and are also important when considering international differences in headache treatment. For example, in Chinese culture, headache is considered an emotional problem or weakness, and men do not frequently admit to suffering from headaches (10). Likewise, headache is perceived as a psychological condition in India and, as of 2008, headache care was not covered by insurance in India for that reason. In Moldova, rates of medication overuse are relatively low, which has been attributed to phobias regarding medication side effects and drug dependency. Furthermore, in Moldova, pain and pain tolerance have a religious significance in that the orthodox tradition considers the attitude to pain as something holy and connected with the spirit of Christianity, the dominant religion in the country (11).

Chronic migraine

CM is a common and disabling disorder that was initially classified in the second edition of the ICHD as a complication of migraine (12). In the ICHD-3 (1) it has its own category under migraine (subcategory 1.3). It is characterized by at least 15 headache days per month for at least 3 months, with at least eight headache days per month that meet criteria for migraine with or without aura, or would have if the patient had not taken an ergot or triptan. When compared to those with episodic migraine, patients with CM are more likely to be disabled, have a lower health-related quality of life, higher levels of anxiety and depression, and greater healthcare resource utilization (13,14).

A 2010 review of population-based based studies examining the prevalence and/or incidence of CM found a global prevalence of 0–5.1%, with estimates generally between 1.4% and 2.2% (15).

Variations in regional prevalence were noted, although it was unclear whether these differences represented actual geographical variations, methodological differences, or differences in the CM definition used in individual studies. CM was most prevalent in the Americas, at up to 5.1%, although there was a large variation between studies (1.3–5.1%). Prevalence in Europe was generally lower (0–2.4%) and varied with the stringency of the CM definition used.

As compared to Europe and the Americas, population-based data from Asia are sparse, and classification criteria vary between studies. A systematic review of CM and CDH in the Asia–Pacific region (16), which included two studies conducted in Taiwan and one study each in China, India, Korea, Malaysia, and Singapore, found a CM prevalence ranging from 0.6% to 1.7%. There were no eligible studies from Australia, New Zealand, or the Pacific Islands.

Management of CM

Few treatments for CM are evidence-based, owing, in part, to the relatively recent recognition of CM as its own diagnostic entity, and the evolution of its definition (see also Chapter 31). The use of topiramate, sodium valproate, gabapentin, tizanidine, and amitriptyline for the prevention of CM is supported by randomized placebo-controlled trials (17–23). In addition, beta blockers, calcium channel blockers, selective serotonin reuptake inhibitors and serotonin and norepinephrine reuptake inhibitors (SNRIs), as well as other medications, are often used on an empirical basis for CM treatment. In 2010, the US Food and Drug Administration (FDA) approved onabotulinum toxin A for the preventive treatment of CM in adults, after publication of results from the PREEMPT (Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy) studies, two large, multicentre, double-blind, placebo-controlled trials (24).

Recently, anti-calcitonin gene-related peptide (CGRP) monoclonal antibodies have emerged as effective treatment for migraine prevention. These disease-specific, mechanism-based medications target the CGRP ligand or its receptor and have demonstrated positive results for episodic and chronic migraine in phase II and phase III studies, with only rare serious adverse events. In addition to their favourable tolerability profile, other advantages over traditional oral preventive medications include an early onset of effect, monthly or quarterly dosing schedule, and their potential for efficacy in patients with MOH (25). Erenumab, fremanezumab, and galcanezumab received FDA approval in 2018. At the time of publication, erenumab and galcanezumab have been approved in Europe, and erenumab has received Therapeutic Goods Administration approval in Australia.

Non-invasive neurostimulation has gained attention in recent years owing to its tolerability, safety, and relative ease of use. As such, various devices have been developed for the treatment of primary headache disorders. Results from two randomized, controlled, double-blind studies assessing non-invasive vagal nerve stimulation (nVNS) for CM prevention have demonstrated safety and tolerability (26,27). While ongoing treatment may reduce headache frequency, larger sham-controlled studies are needed to better assess its role in CM treatment. Open-label studies investigating transcutaneous supraorbital nerve stimulation in CM prevention have shown significant reductions in headache days and use of analgesics, as well as a high percentage of satisfaction and intent to continue with treatment (28,29). However, there have been no randomized, double-blind, sham-controlled studies for this population.

In a 2004 study by Tepper et al. (30), patterns of practice for migraine prevention among headache specialists in Europe and North America were assessed by questionnaire. A high level of agreement was found in management strategies and prevention for patients with three or more headaches per month, and more than 60% stated that acute medications should be used on no more than 8 days per month. In addition, the vast majority of physicians used beta blockers as a first-line preventive treatment. Topiramate, amitriptyline, and calcium-channel blockers were the most frequently used second-line agents, and valproate, newer antidepressants, and methysergide were third-line agents.

Despite an agreement among headache specialists regarding the use of acute and preventive medications, migraine remains undertreated around the world. The International Burden of Migraine Study (IBMS) (6) found that less than one-third of CM patients in five European countries (UK, France, Germany, Italy, and Spain) reported the use of preventative medications. Similar rates of undertreatment have been reported in the USA (31,32) and Canada (32), although, overall, the use of preventive medications was higher in the USA than in Canada, with a significantly higher percentage of US patients with CM receiving an antiepileptic (32). More recent studies in the USA (33,34) indicate that migraine persists as an underdiagnosed and undertreated public health problem. Acute and preventive migraine treatments remain underused; those who received prevention discontinued it by the end of the first year and were unlikely to switch to other preventive treatments.

Eurolight, an initiative supported by the European Commission Executive Agency for Health and Consumers and conducted by Lifting the Burden, utilized a cross-sectional survey in 10 countries (Austria, France, Germany, Ireland, Italy, Lithuania, Luxembourg, the Netherlands, Spain, and the UK) to compile data on headache disorders, headache-attributed burden, and the related use of medications and medical services. Recently published evidence indicates that even in wealthy European countries, migraine remains undertreated, with too few migraineurs consulting physicians. Of those who do seek medical care, too many see specialists and migraine-specific medications still remain underused (35).

In a Taiwanese clinic-based study (36), the rate of preventive medication usage for CM was notably higher (48.5%) than in most European countries, although this may be attributed to differences in study design (i.e. clinic-based vs population-based samples). Nonetheless, fewer than half of the patients with CM in the study were on a preventive medication, once again underscoring the undertreatment of patients with CM.

European data from the IBMS also showed that the percentage of patients with CM reporting inpatient hospitalizations for migraine treatment was significantly higher in the UK (8.8%) compared with any other country (0% for France, 3.8% for Germany, 3.6% for Italy, and 3.6% for Spain). Although inpatient management is generally associated with higher costs, the authors suggested that the high percentage of patients with CM receiving inpatient migraine treatment in the UK might actually reflect better awareness and management of CM (6). There are two inpatient scenarios in the USA. Non headache specialists sometimes admit patients with CM with an exacerbation for 3 days of an opiate. A limited number of headache specialists have excellent inpatient programs for CM, including detoxification if needed, intravenous (IV) therapy, preventive therapy, and an interdisciplinary approach. This is a costly, but very helpful,

therapy from which many improve and it usually reduces the cost of care over time.

Acute treatment

An assessment of medications used in the acute treatment of episodic and chronic migraine in the USA (31,37) found that migraine-specific treatments were used by only a minority (22%) of participants with CM. The vast majority (97%) of migraine-specific medications were triptans, most of which were oral formulations (83%). Non-specific medications included opiates (20.8%), butalbital-containing compounds (13.5%), and over-the-counter (OTC) medications, including paracetamol (35%), combination OTCs (62.8%), and NSAIDs (43.1%). Barbiturates and opioids were more commonly used in CM than in episodic migraine (EM), while NSAIDs and combination OTCs were used more frequently in EM than CM.

Similar patterns of acute medication usage in the treatment of migraine have been found in other countries. In a population-based study (38) of migraineurs in six Latin American countries (Mexico, Argentina, Ecuador, Venezuela, Brazil, and Colombia), of which 15% reported having > 15 migraine headache days per month, a widespread pattern of self-treatment with OTC medications was observed. Paracetamol and salicylates were the most frequently used medications, followed by NSAIDs and dipirone (metamizol, a non-narcotic analgesic). Ergot derivatives were used by fewer than one-third of migraineurs in Argentina and Ecuador, even though they are easily accessible, and triptan use overall was low (0–1.4%).

Studies evaluating patterns of triptan use in the Netherlands (39), Italy (40,41), and France (42) also indicated suboptimal acute treatment of migraine patients, with low rates of triptan and ergotamine utilization demonstrated in the studies. As in the Latin American study, the low rates of specific treatment in the European studies were attributed to underdiagnosis and/or undertreatment of migraine.

Sumatriptan has also been shown to be underutilized in Taiwan, and many neurologists had never prescribed it to their migraine patients (8). This may be attributed to the higher cost and strict regulations of the National Health Insurance, resulting in comparatively higher usage of NSAIDs or ergotamine for acute treatment.

Medication overuse headache

MOH is the generation, perpetuation, worsening, or maintenance of chronic headache resulting from frequent and excessive intake of medications used for acute headache treatment (see also Chapter 31) (1). MOH only occurs in patients with a prior headache history; the medication overuse itself does not cause the development of headache de novo. Migraineurs are particularly susceptible to the development of CDH associated with medication overuse (43), although patients with CTTH, HC, post-traumatic headache, NDPH, and others may also overuse symptomatic headache medications. Medication overuse is considered the most important aggravating factor in the progression from EM to CM (44).

MOH is one of the most common forms of CDH. The population-based 1-year prevalence of MOH in different countries ranges from 0.7% to 1.7%, with a female preponderance of 62–92% (45–50). Among patients aged > 65 years, the prevalence rates ranged between 1.0% in Taiwan (10) and 1.7% in Italy (51). MOH affects > 50% of patients in US headache clinics and up to 30% of patients in European headache centres (52–54). By contrast, only 3.1% of patients in a headache clinic in India were diagnosed with MOH (55).

MOH can be caused by a number of medications used for acute treatment, including ergotamine derivatives, barbiturates, triptans, simple and combined analgesics, opioids, benzodiazepines, and caffeine. Although the frequent use of NSAIDs is associated with progression to MOH in migraineurs with a high baseline migraine frequency, NSAIDs may actually be protective in patients with low baseline headache frequency (56). However, a causal role for NSAIDs in the chronification of headache has not been established (57).

Patterns of MOH in different countries depends on the availability and accessibility of acute care medications. Until the introduction of triptans, the drugs most commonly associated with MOH in the US were combination analgesics containing butalbital (a short-acting barbiturate), caffeine, and aspirin with or without codeine (58). In European countries combination analgesics with codeine or caffeine, or ergots combined with codeine, were the most frequently used acute medications (59,60). The removal of ergotamine from some markets resulted in a period of high barbiturate use until barbiturate-containing medications for migraine were also removed from the market. Barbiturate-containing medications, such as combination analgesics with butalbital, continue to be available in the USA and, like opioids, are associated with an overall increased risk of transformed migraine, at any frequency of use (56).

The introduction of sumatriptan in the 1990s led to a shift in patterns of MOH, as demonstrated in a German prospective study in which triptans, despite their high cost, were found to cause MOH in many more cases than ergots. The study also showed that triptans caused MOH faster and at lower doses than other drugs such as ergots and analgesics (61). Similarly, in a chart review of 1200 patients at a large US headache centre between 1990 and 2005, a significant decrease in MOH attributed to ergotamine and combination analgesics was noted, while the frequency of MOH due to simple analgesics, combination of acute medications, and triptans increased significantly. The frequency of opioid overuse headache did not change significantly over the time period (54).

In countries where sumatriptan and other triptans were introduced more recently, MOH associated with triptans is less common. Triptans were first introduced in Japan in 2000; in a 2007 retrospective study of 47 patients with MOH (62), only one patient overused triptans. Combination analgesics, none of which contained codeine or barbiturates, were most commonly associated with MOH. Similar results were seen in a larger, headache clinic-based study with 276 patients with MOH (63).

The cost of triptans also remains a prohibitive factor in some countries such as India, where ergotamine remains the most common medication associated with MOH (55). Combination analgesics and opioids are limited in availability and short-acting barbiturates are not used for acute headache treatment in India. Those with headaches are usually more inclined to try topical pain balms and alternative therapies initially before resorting to painkillers, and this has been proposed as a reason for the lower incidence of MOH in India compared with Western countries (55).

Management of MOH

Treatment of MOH involves several steps: complete weaning of overused medications, initiation of preventive treatment and/or behavioural or non-drug preventive strategies, establishing limits on

future acute medication intake to prevent MOH relapse, and education of the patient and family (see also Chapter 31). Education is vital; if the patient is not convinced that the therapy is reasonable, the results will not be good. Treatment may be carried out in a number of different settings, depending on the individual patient's clinical picture. When choosing a treatment plan, multiple factors are considered, including the duration and severity of headache attacks, the number of overused medications and their doses, and comorbid medical and psychiatric conditions. Outpatient treatment may be adequate for relatively uncomplicated patients, but infusion therapy (inpatient or outpatient) or integrated programmes (day hospital or inpatient programme) may be required for those with more severe headaches or those that use tranquilizers, opioids, or barbiturates, particularly in higher doses. All of the above may be necessary, with or without onabotulinum toxin A, for the most challenging patients (64).

The weaning of offending medications can be done slowly or rapidly. Slow weaning is usually done over the course of 4–6 weeks, during which preventive treatment is established. A course of steroids may be helpful in refractory situations. Rapid weaning involves the abrupt discontinuation of the offending medication, along with a 7–10-day oral or IV bridge to treat headaches and reduce withdrawal symptoms. Repetitive IV dihydroergotamine (DHE), based on the Raskin protocol, is typically used as a bridge in the USA (65). Other options such as NSAIDs, steroids, IV valproate, triptans, chlorpromazine, metoclopramide, and DHE nasal spray have been described, although none has been established in randomized, placebo-controlled trials. Patients who overuse high-dose opiates, barbiturates, and/or benzodiazepines require special, extended weaning protocols (64).

Although detoxification has traditionally been recommended before initiating preventive treatment in patients with CM and MOH, some have suggested that this is not necessary (66), on the basis of several studies showing the effectiveness of topiramate and onabotulinum toxin A in patients with CM and MOH (24,67–70). This, however, remains a topic of active debate (66,71,72). The success of the monoclonal antibodies to CGRP or its receptor in treating MOH adds new data to the debate.

Withdrawal strategies are varied and no randomized studies have compared abrupt withdrawal treatment with tapered protocols. Treatment strategies may differ between countries, as well as between centres in the same country. In the November 2008 issue of *Cephalalgia*, headache specialists from Moldova (11), Scandinavia (53), India (55), Japan (63), Germany (73), Spain (74), Taiwan (75), and Canada (76) discussed their experiences with MOH and its treatment. Despite the differences in specific protocols, some general themes emerged. Abrupt withdrawal of offending medications in an outpatient setting is the most common initial strategy (53 55,63,73,74), although inpatient treatment is typically used for patients who overuse opioids, fail outpatient withdrawal, or have significant psychiatric comorbidity (53,63,73,74). Most specialists also recommended a multidisciplinary approach with an emphasis on patient education, behavioural treatment, and the identification of psychiatric issues (53,55,63,73,74,76). Many of these measures have also been incorporated into the guidelines for MOH treatment issued by the European Federation of Neurological Societies (77).

Country-specific MOH protocols are described in further detail as follows.

Scandinavia

At the Danish Headache Center, abrupt discontinuation of all acute medications is recommended and patients are maintained in a medication-free state for 2 months (78,79). Outpatients attend a 'headache school' in which detailed, standardized information is offered in a group of 6–8 patients, while inpatient treatment is offered to severely affected patients with comorbidities, high analgesic intake, including opioids, and failed outpatient treatment. Levomepromazine or Phenergan are used as rescue treatment during withdrawal, and a 5-day course of phenobarbital or methadone is used in patients with severe opioid overuse headache. Good outcomes have been described with this strict 8-week withdrawal programme (53).

India

Outpatient withdrawal is the most common strategy for MOH detoxification in India. Inpatient withdrawal is undertaken relatively infrequently as patients in India are unwilling to be admitted for headache treatment, for various reasons. Although DHE is not available in any form in India, some patients are able to procure it from elsewhere. Parenteral chlorpromazine, valproate, and steroids are used for inpatients who cannot obtain DHE. All inpatients and outpatients are started on amitriptyline 10 mg daily, and also undergo cognitive behavioural therapy. Treatment strategy is based on patient preference rather than the overused medication (55).

Japan

In Japan, abrupt outpatient withdrawal is the recommended method of detoxification, although inpatient withdrawal is considered in difficult cases and tapering outpatient withdrawal is the least preferred option. Prevention aimed at the underlying headache disorder is often initiated during withdrawal. Tricyclic antidepressants such as amitriptyline are used for both migraine and TTH, while lomerizine, a calcium channel blocker, is used for migraine. Anticonvulsants are also used. In addition, oriental herbal medicine, acupuncture, and headache exercise may be offered in refractory cases (63).

Germany

In Germany, MOH is treated by a multidisciplinary team comprising neurologists, psychologists, and physiotherapists. Abrupt drug withdrawal is the treatment of choice, which may be done through inpatient programmes or in an outpatient setting or day clinic. Outpatient withdrawal is recommended for highly motivated patients who do not overuse opioids or tranquilizers, while inpatient detoxification is undertaken in those who overuse opioids, fail outpatient withdrawal, or have significant psychiatric comorbidity. Most patients are treated with 100 mg oral prednisone for the first 5 days after medication withdrawal, and 500–1000 mg IV aspirin is usually given, if necessary, for rescue treatment (73).

Spain

In 2006 the Headache Group of the Spanish society of Neurology published local guidelines for the treatment of MOH. Detoxification is usually done abruptly, in an outpatient setting. Daily NSAIDs (e.g. sodium naproxen 550 mg q8h with gastric protection) are given for about 15–30 days, and triptans are used for moderate-to-severe headaches for up to 2 days if they are not the overused drug. Preventive treatment is started early and is based on the underlying headache

disorder. Amitriptyline, 20–50 mg nightly, is used in patients with underlying TTH. Migraine patients are prescribed beta blockers with nocturnal amitriptyline, or an antiepileptic. Topiramate and valproic acid are both used, but topiramate is generally preferred. For patients who do not respond to the above regimen, a combination of a beta blocker and an antiepileptic is prescribed, and botulinum toxin type A may be added as well (74).

The pharmacological protocol for inpatient management is as follows: (i) IV methylprednisolone, at least 80 mg every 24 h, for 5–7 days; (ii) IV valproate 400–800 mg every 12 h for 3–5 days, then oral prevention with 500–1000 mg/daily; (iii) IV metoclopramide; (iv) short treatment with either benzodiazepines or neuroleptics (1–2 weeks); and (v) NSAIDs (after the steroids) and triptans as in the outpatient protocol. IV DHE is not available in Spain (74).

While the concept of MOH and recommendations for limitation of acute treatment have been widely accepted for some time, there is ongoing debate over whether MOH is truly a secondary headache disorder or whether the overuse of analgesics can be viewed as an epiphenomenon to a progressive primary headache disorder. As evidence from high-quality, large, well-designed randomized controlled clinical trials on MOH is lacking, some headache specialists have called for a critical appraisal of MOH in each individual patient, suggesting that frequent use of acute headache medications 'should be viewed more neutrally, as an indicator of poorly controlled headaches, and not invariably a cause' (80,81).

Chronic cluster headache

Cluster headache is a TAC that presents with severe, unilateral pain accompanied by ipsilateral cranial autonomic features. Individual cluster attacks last 15–180 minutes and range in frequency from one attack every other day to eight attacks daily during cluster periods. Patients with CCH have attacks that occur for more than 1 year without remission or with remissions lasting less than 3 months (1).

Compared to migraine, the prevalence of cluster headache is very low and little is known about the population-based epidemiology of cluster headache. A meta-analysis of population-based studies of cluster headache published up to 2007 found that the 1-year prevalence varied significantly between studies, ranging from 3 to 150 in 100,000. The pooled lifetime prevalence was 0.12% and the ratio of episodic versus chronic CH was 6.0. While regional differences in cluster headache prevalence were difficult to establish owing to the small number of studies, trends suggested that in the more northern countries the prevalence rates were higher than in those countries closer to the equator (no studies from countries south of the equator were available) (82). Since then there have been only a few population-based studies, which showed a prevalence of 87 per 100,000 in the Republic of Georgia (83), 1.3% in rural Ethiopia (84), and 41.4 per 100,000 in Brazil (85).

The treatment of CCH requires acute, transitional, and preventive treatment (see also Chapter 18). Acute therapy includes oxygen inhalation, triptans (nasal spray or injectable), and DHE, while transitional treatment generally involves steroids or an occipital nerve block. Patients with lengthy cluster periods or CCH require preventive treatment that can be used on a long-term basis. Verapamil is usually used as a first-line preventive treatment in CCH. Other options include lithium, topiramate, divalproex sodium, gabapentin, and melatonin.

Surgical options, which include occipital nerve stimulation (ONS) and deep brain stimulation (DBS), may be considered in patients with medically refractory CCH. A review of ONS in drug-resistant CCH (86) found that occipital nerve stimulation is effective in about two-thirds of patients (> 50% frequency reduction). Hypothalamic DBS for CCH is generally reserved for patients with daily or near-daily attacks that are refractory to all pharmacology, including combination regimens. It was introduced by Leone et al. in 2001 (87), with a case report in which cluster attacks were eliminated in a patient with CCH after stereotactic positioning of an electrode followed by stimulation of the posterior inferior ipsilateral hypothalamic grey matter. Since then, DBS has been successful in reducing or preventing cluster attacks in approximately 50–60% of medication-refractory CCH patients treated at experienced centres (88–91). DBS for CCH is most well established in Italy, where the pioneering procedures were performed at the Istituto Neurologico Carlo Besta in Milan. Owing to potential serious adverse effects, DBS should only be considered in the most severely disabled patients after all other medications and non-invasive therapies have been trialled. More recently, sphenopalatine ganglion stimulation has emerged as another potential surgical option for both acute and preventive treatment of medically refractory CCH (92–94).

nVNS, when used as acute or preventive CCH treatment, demonstrated a significant reduction in weekly attack frequency in a prospective, open-label randomized study in which nVNS combined with standard of care was compared with standard of care alone (95,96).

Conclusion

Among international headache specialists there appears to be broad agreement that treatment of CM generally begins by identifying whether MOH is present. If so, it is treated accordingly, and preventive treatment is usually initiated early. International headache specialists use a number of preventive medications, most commonly including tricyclic antidepressants, topiramate, valproate, and beta blockers. Botulinum toxin has been increasingly used, although its application is limited by cost and reimbursement issues in many countries. Most respondents use onabotulinum toxin A, and that is the toxin with the most evidence and the only one with FDA approval for CM treatment. The anti-CGRP receptor or ligand monoclonal antibodies have only recently been introduced in some countries. Given their efficacy and tolerability as shown in multiple studies, their role in the management of episodic and chronic migraine as well as MOH in clinical practice is eagerly anticipated.

Abrupt withdrawal of overused medications in the outpatient setting is the preferred treatment of MOH, and inpatient treatment is reserved for those who fail outpatient treatment, suffer from significant psychiatric comorbidity, or overuse significant amounts of opioids, benzodiazepines, or tranquilizers. Specific pharmacological protocols vary, depending on the medications overused in a particular country, as well as the medications available for use in detoxification. Most headache specialists also agree that patient education and behavioural treatment are cornerstones of MOH management. Early clinical experience with the CGRP antibodies

in treating all types of migraine and especially MOH shows promise. It appears that outpatient treatment with these new therapies may help patients to use fewer acute care medications as their headaches decrease.

CCH treatment around the world generally comprises preventive treatment with verapamil or lithium, and injectable sumatriptan, intranasal zolmitriptan, and oxygen therapy are typically used for acute treatment. Surgical options may be considered for medically refractory cases but are not widely available; experience with these procedures has been predominantly in Europe and began in Milan, Italy. We learned that CCH is very rare in Taiwan and other Asian countries.

CM and MOH are disabling conditions associated with significant personal, societal, and economic burdens. However, both remain under-recognized and undertreated worldwide. Increasing the awareness and treatment of CDH and its subtypes through research and public health policies will reduce the societal and economic costs associated with the disorder. In particular, promoting research in developing countries should be a priority as much of the world lives in LAMI countries where the burden of CDH may be high, but resources addressing the problem are scarce.

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Appendix 32.1 Comments from international headache specialists on the treatment of chronic migraine

The prophylactic agents for episodic migraine most commonly prescribed by Australian general practitioners are pizotifen and propranolol (97). Most patients with chronic migraine would also be treated with these agents initially. Neurologists would often move on to other agents, including topiramate, sodium valproate, and amitriptyline, as would be the case elsewhere. Methysergide is no longer available. Candesartan is popular with a number of neurologists; there is now a better-established evidence base to support its use. It is effective in a proportion of cases and is well tolerated in most patients (98). Onabotulinum toxin A has become increasingly widely used, especially since being subsidized by the Pharmaceutical Benefits Scheme, which makes it affordable.

Dr Richard Stark, Australia

My first step is to ensure there are no obvious precipitating factors such as analgesic overuse or the contraceptive pill, and to manage depression with tricyclic antidepressants. Many patients respond to topiramate, which is often reasonably well tolerated if the dose is built up slowly from 12.5 mg daily towards 100 mg daily or more. There are occasional patients who are referred to my colleague for botulinum toxin A injections.

Dr Richard Peatfield, England

The general approach comprises clear and emphatic patient education, with handing out of written material, especially in tertiary centres, aggressive withdrawal of overused symptomatic medications, sometimes with a bridge treatment using steroids as Brazil doesn't have dihydroergotamine in injectable preparations, initiation of preventive therapies usually with rational combination of drugs, rescue treatment, and enforcing adherence to a programme of exercise and sleep hygiene (99).

Specifically for chronic migraine or migraine and medication overuse headache, in addition to prevention with a combination of pharmacological agents, acute treatment is prescribed with a maximum frequency of twice a week. Two classes of drugs are simultaneously prescribed and even for severe attacks a written prescription for injectable triptan + rectal non-steroidal anti-inflammatory agents is provided with orientation of seeking emergency departments willing to administer the right medications (chlorpromazine, steroids, and *not* only simple analgesics and opioids). We enforce the prohibition of using opioids despite the stubbornness of some centres in giving tramadol to patients. Botulinum toxin is not used in our centre as most of our patients present with unsuccessful previous attempts and we don't think it has been used other than with commercially driven approaches by most health professionals. Additionally, we push the patients to adhere to a 4-day per week 1-hour-long fast walking programme and follow-up the patients every 1–2 months and ask them to keep a detailed headache calendar. We are confident in the success of our approach as a recent Masters' degree study carried out in our centre demonstrated a higher than 80% compliance rate (100).

Dr Abouch Krymchantowski, Brazil

Twenty to 37% of chronic daily headache (CDH) patients in Taiwan were found to have medication overuse in population-based studies (10,45,101), while a clinic-based study found that medication overuse headache could be diagnosed in up to 48% of CDH patients (102). Most of the patients with medication over use headache (MOH) are actually chronic migraine patients. Detoxification is undertaken either in the hospital or in the outpatient setting, depending on patient characteristics [see 'Medication overuse headache']. Like the practices in many countries, migraine prophylactic agents are always prescribed simultaneously with acute abortive treatment and maintained for months.

Dr Shuu-Jiun Wang, Taiwan

Chronic migraine is most commonly treated by topiramate or by botulinum toxin. This depends on the preference of the doctor and the patient. Both are reimbursed by all health insurances. Many doctors also give amitriptyline, duloxetine, or mirtazapine, either alone or in combination with topiramate and botulinum toxin. If medication overuse is present, withdrawal treatment is also always considered. In only very few centres, vagal nerve stimulation is offered. At the time of writing this comment, the monoclonal antibody erenumab has been approved also for the treatment of migraine, including chronic migraine, and is being prescribed more and more. The monoclonal antibodies galcanezumab and fremanezumab will also be approved for migraine, including chronic migraine, in short time. The antibodies are fully reimbursed by all health insurances if at least four oral drugs and botulinum toxin were not efficacious.

Dr Stefan Evers, Germany

The first choice for treating chronic migraine in Estonia is generally either tricyclic antidepressants, topiramate, or non-cardioselective beta blockers. In case of intolerability or lack of efficacy, candesartan or SNRIs (venlafaxine, duloxetine) are in use. Failure to achieve substantial effect leads to consideration of an injectable treatment with onabotulinum toxin A or erenumab; however, the high price and absence of reimbursement of these treatment options limit their usage considerably.

Dr Mark Braschinsky, Estonia

In our practices we follow the 2012 Italian Guidelines for Primary Headaches (103), which we helped to write. Different from the US, flunarizine is available in Italy and it is considered among the first-line drugs for the prophylaxis of migraine. Subcutaneous sumatriptan is difficult to find and pizotifen has recently become unavailable.

Dr Giorgio Zanchin, Federico Mainardi, Italy

The Canadian Headache Society Guidelines for Migraine Prophylaxis provide a detailed approach to the management of many scenarios. They can be accessed at www.headachesociety.ca (104). The acute guidelines will take a similar approach. Whether the guidelines will have any impact on practice

remains to be seen. Previous guidelines from 1997 (105) had a measured 2% impact on practice patterns.

Although onabotulinum toxin A has been approved by Health Canada for the indication of chronic migraine, the fee for the injection is not covered for this indication, except in Quebec.

Dr Marek Gawel, Canada

In the headache centre of the Leiden University Medical Center, we rarely see patients with chronic migraine (CM) who are not overusing acute anti-headache medications. It was shown that patients with medication overuse and underlying migraine benefit greatly from withdrawal therapy, especially when combined with guidance by a specialized headache nurse. Current treatment of CM in our centre consists of withdrawal of overused medication [as described under 'Medication overuse headache']. This means acute withdrawal of all acute headache medication and phasing out of prophylactic treatment with no escape medication during the withdrawal period. During this period a headache diary is filled out by the patient. After two or three months of the withdrawal phase (two for triptans, three for analgesics or combination of analgesics and triptans), treatment for remaining migraine attacks is started. Patients are strongly advised not to treat more than two migraine attacks per month, each during a maximum of 2 days, using a maximum of two triptans per day (2 × 2 rule). This way, recurrence of triptan overuse is prevented. Patients with two or more attacks per month are also advised to start prophylactic treatment, to reduce the number, severity, and duration of attacks. This will make it possible for the patient to fulfil the rule of maximum of 2 × 2 acute treatments per month.

The question remains, however, whether prophylactic treatment should be started during withdrawal. Recently, trials using onabotulinum toxin A have been shown to elicit a small but significant response in chronic migraineurs, who were not withdrawn from medication overuse (106,107). As our current treatment of CM (withdrawal with support of a headache nurse) is inexpensive and seems adequate, treatment with onabotulinum toxin A only seems unwise. However, there might be a role for it as a prophylactic treatment during the withdrawal period, using it to bridge the worst part of the withdrawal effects, and it may further reduce the number of headache days after the withdrawal. We have recently finished a trial to investigate this further (CHARM (CHronification And Reversibility of Migraine) trial). In this trial, we show that onabotulinum toxin A does not afford any additional benefit over acute withdrawal alone (108). We thus strongly recommend that withdrawal of acute medication should be tried first before initiating more expensive treatment with onabotulinum toxin A.

A new treatment class that also will become available for CM are the CGRP antibodies. However, also for trials with this new type of preventive medication, CM patients with medication overuse headache (MOH) were included. We strongly recommend a trial showing that anti-CGRP-R antibodies have an additional effect on withdrawal in CM + MOH patients.

Drs Judith Pijpers, Dennis Kies, and Gisela Terwindt, The Netherlands

In my practice, chronic migraine (CM) is the most frequently seen primary headache disorder. It is very common to have comorbid medication overuse. Causality can be quite difficult to ascertain; therefore, I educate the patient regarding the issues, advise on the limits of acute medication, and add effective preventives.

Onabotulinum toxin A was the only Food and Drugs Administration (FDA)-indicated treatment for CM until the new CGRP antibodies became available; many patients are specifically referred for consideration of onabotulinum toxin A therapy. It is frequent that the insurer will require that 'medical necessity' be shown by not only having a diagnosis of CM, but also that the patient has been tried on several 'standard' preventives. Of course, none of these is FDA-indicated for CM. Of the various medicines that are frequently advised, only topiramate has clinical data supporting its efficacy for CM. Antidepressants, beta blockers, and calcium channel blockers have no substantial evidence in their favour for the preventive management of CM.

When I do see a patient for onabotulinum toxin A therapy, I tend to incorporate both PREEMPT data and my own experience as an injector for nearly 30 years. This entails assessment of possible dystonic features, myofascial features such as head forward posture, or possible temporomandibular disorder components. Thus, I assess whether there are areas of pain that are prominent on one side compared to the other, bruxism, or clenching, or whether one side of the neck or shoulder is more sore or tender. This is followed by physical examination, looking for features that would guide dosing in an asymmetric fashion. My average dose for Botox treatment is about 180 units. I typically have the patient follow-up with my physician assistant in a month or so for reassessment, and the assistant will take care of any interval prescriptions. The patient schedules their 12-week re-injection visit at the time they leave from their injection.

Now, with the advent of monoclonal antibodies indicated for migraine prevention, with evidence for benefit including patients with CM, I have started to incorporate them into our treatment algorithm. Trial results have generally shown effectiveness comparable to that with onabotulinum toxin A, with side effects that thus far have been comparable to placebo. The long-term effects of chronic CGRP blockade are, of course, being closely watched.

Dr Jack Schim, USA

Appendix 32.2 Comments from international headache specialists on the treatment of medication overuse headache

Patients with medication overuse headache (MOH) are either hospitalized for detoxification or treated in the outpatient clinic, depending on their severity, medical comorbidities, and preference. In outpatient treatment, oral DHE, prochlorperazine, and non-steroidal anti-inflammatory drugs are commonly prescribed for detoxification. For inpatient treatment, intravenous prochlorperazine has been commonly used as there is no available injection form of dihydroergotamine in Taiwan. In our experience, repetitive intravenous prochlorperazine treatment is highly effective in aborting withdrawal headaches (109). Intravenous magnesium sulfate, ketorolac, methylprednisolone, sodium valproate, lidocaine, or olanzapine are the other alternatives.

In Taiwan, prophylactic agents, including propranolol, flunarizine, amitriptyline, valproic acid, or topiramate, are given to MOH patients after detoxification for a period of at least several months and are tapered if their headache symptoms improve substantially (75).

Dr Shuu-Jiun Wang, Taiwan

In Australia, unfortunately, combination analgesics containing up to 15 mg codeine per tablet have been available without prescription (until February 2018 when they became prescription-only) and combinations of up to 30 mg per tablet are prescribed regrettably often for frequent headaches by general practitioners. Thus, we have to deal with many patients overusing codeine in substantial amounts. Withdrawal in such patients is associated with a great increase in headache severity, so that outpatient protocols are often unsuccessful. On this background, the use of intravenous lignocaine (lidocaine) has become popular as a means of managing medication withdrawal (110,111). In our experience, lignocaine provides better relief in some patients than dihydroergotamine and in our department it is the first-line approach in patients requiring inpatient detoxification. Cardiac complications have not been an issue, but neuropsychiatric symptoms may occur if the dose is pushed too high (112). We have generally used a conservative dose of 2 mg per minute and rarely see such problems, but occasionally the dose must be increased to obtain a better response. Alternatively, if serum lignocaine levels can be obtained promptly, the dose can be adjusted accordingly.

Dr Richard Stark, Australia

One of the problems with the UK's National Health Service is a dire shortage of beds for inpatient analgesia withdrawal and we have to try to persuade the patient to stop taking medication while still at home. In the UK, opiates and particularly codeine, dihydrocodeine, and, until recently, dextropropoxyphene were on sale to the public in small doses and most abusing patients take paracetamol/codeine combinations of some type. Barbiturates have always been prescription drugs and are not a problem; there are a few patients who take excessive quantities of triptans, although there are usually financial restraints on general practitioners that keeps the number of prescription per month down. I find there are a number of 'addictive personalities' who reappear 2 or 3 years after withdrawing one drug taking another; we have no easy answers!

Dr Richard Peatfield, England

Medication overuse headache is always treated first by withdrawal therapy. About 50% of the patients still undergo inpatient withdrawal therapy, but this rate is decreasing. Most doctors start prophylactic treatment early in the withdrawal period. During withdrawal therapy, steroids are given in most clinics. Also, naproxen, aspirin, and metoclopramide are given as acute medication. Patients are followed up regularly after withdrawal. We do not use dihydroergotamine infusion.

Dr Stefan Evers, Germany

Despite some advances in healthcare professionals' awareness in the field of medication overuse headache, it is still largely under-recognized, underdiagnosed, and undertreated in Estonia. The vast majority of patients are managed in Tartu University Headache Clinic, where treating this group of patients is complex, starting with patient education by a headache specialist and headache nurse, and includes detoxification, initiation of prophylactic medication, and cognitive–behavioural treatment. If the outpatient approach fails, patients are admitted to the neurology department, where steroids are used.

Dr Mark Braschinsky, Estonia

Medication overuse headache (MOH) is a condition often seen in Leiden Univesity Medical Center. The patients receive two diagnoses: (i) MOH (following ICHD criteria); and (ii) the presumed underlying primary headache syndrome. Substances most often overused are simple analgesics, non-steroidal anti-inflammatory drugs, triptans, or combination analgesics, such as paracetamol with caffeine. Overuse of opioids, barbiturates, or ergotamine is rarely seen in the Netherlands.

Regular treatment for MOH is acute cessation of all oral anti-headache medication and caffeine, as well as the phasing out of any prophylactic medication. The duration of this withdrawal period is determined by the type of substance overused. For analgesics, combination analgesics and combinations of analgesics and triptans, or caffeine, withdrawal is 3 months. For triptans the withdrawal period is 2 months. During this period, no escape medication is allowed. No prednisone is given. During the withdrawal period, patients are regularly counselled by a trained headache nurse, who is available for support and gives tips and advice on how to get through the withdrawal period. Patients are not hospitalized during the withdrawal phase.

A recent (unpublished) study conducted in our centre showed that guidance by our headache nurse significantly increased the chance of successfully withdrawing from overused medications from 61% to 73%. Patients with migraine and medication overuse had a larger reduction in headache days than patients with underlying tension-type headache (mean relative reduction in headache days: 56.1% vs 26.0%) (unpublished data).

Drs Dennis Kies and Gisela Terwindt, The Netherlands

For medication overuse headaches, I classify patients into five categories: (i) daily acute medication intake without harm; (ii) toxic/side effects from daily acute medication intake; (iii) excessive acute medication intake due to or associated with psychiatric comorbidity; (iv) rebound headache due to analgesics causing allodynia or increase in pain sensitivity; (v) acute medication abuse (fitting Diagnostic and Statistical Manual of Mental Disorders, 5th Edition diagnostic criteria for substance abuse disorder).

In patients in the first group, daily analgesic intake is just a consequence of having daily headaches; there is no rebound effect. A preventive medication is started and the patient withdraws analgesics naturally. Usually no significant comorbidity is diagnosed and washout is not necessary. In group 2, patients are taking an excessive amount of daily medication and having side effects from the medication, so the analgesic should be abruptly discontinued and an inpatient programme may be needed. In group 3, screening for mood disorders (bipolar expected to be common), high anxiety levels (generalized anxiety disorder, panic, phobias, post-traumatic stress disorder may occur), compulsivity with or without obsessive–compulsive disorder, or attention-deficit hyperactivity disorder, is carried out. Cephalalgiaphobia is common in those patients. Psychiatric comorbidity should be addressed, and treated with medication and non-pharmacological approaches. In group 4, acute medication class should be changed or its use avoided; prevention should be started currently with washout strategies. In group 5, a substance abuse behaviour is found, and other substances are commonly abused too; the patient should be managed in line with substance abuse guidelines.

Dr Mario Peres, Brazil

Appendix 32.3 Comments from international headache specialists on chronic cluster headache

I am performing more magnetic resonance imaging scans to exclude pituitary and other comparable diseases in patients without a very long history of episodic cluster headache. I always emphasize prophylaxis and would try verapamil first (building up from 120 mg q8h towards 240 mg q8h, or perhaps even slightly more), monitoring the QT interval on the electrocardiogram. If that does not work, I am fairly liberal with lithium carbonate in chronic cluster patients, using the proprietary long-acting preparation Priadel 400 mg q12h in the first instance and increasing it weekly to a maximum of 800 mg q12h in patients who do not respond, trying to get the level to just above 1 mmol/l. There is a good domiciliary oxygen delivery service in England, and I try to arrange for cluster headache patients to have oxygen cylinders, 9 l/minute regulators and 100% masks to use at home, with the zolmitriptan nasal spray (it tastes better than sumatriptan and there is good evidence for its effectiveness) for attacks away from home. In my experience, there is no place for oral triptans or other analgesics.

Dr Richard Peatfield, England

For chronic cluster headache we use the combination of verapamil, lithium, and ergotamine in over 90% of our cases. Because we believe that long-acting verapamil formulations (120 mg and 240 mg) are not as effective as the usual 80 mg presentation, we may prescribe up to three 80-mg tablets every 8 hours, which has shown effectiveness among once-refractory verapamil users. Very rarely other drugs are prescribed. Injectable sumatriptan and/or oxygen inhalation is our most common approach for the acute treatment. Despite current phytotherapy and hormonal suggestions of therapies, we don't believe they may be effective. Neuromodulation with electronic devices are recently arriving in Brazil and robust personal experiences are still not available.

Dr Abouch Krymchantowski, Brazil

Dissimilar to the high prevalence in Western countries, there are very rare patients with chronic cluster headache in Taiwan (113) as in other Asian countries, such as Japan (114) and China (115). Hence, our experience in this subset of patients is limited.

Dr Shuu-Jiun Wang, Taiwan

Chronic cluster headache is treated by verapamil in a dose as high as needed or as tolerated.

Many patients receive steroid treatment from time to time (over 2 weeks, on average). In frustrating cases, topiramate (dose as high as needed or tolerated) and botulinum toxin (dosing as in chronic migraine) are used. In clinical trials, occipital nerve stimulation, sphenopalatine ganglion stimulation, and vagal nerve stimulation are offered in a few centres.

Dr Stefan Evers, Germany

The first choice for cluster headache prophylactic treatment is verapamil. In case of intolerability or lack of efficacy second choice medications include amitriptyline, topiramate, and sometimes other anticonvulsants, like lamotrigine and alpha-2-deltas. Lithium is not available in Estonia. Despite the technical availability of neuromodulation, it is not used owing to the absence of reimbursement and national guidelines for treating cluster headache.

Dr Mark Braschinsky, Estonia

High doses of verapamil and corticosteroids have been effective in a few cases of chronic cluster headace, one of which was described in a case report presented in abstract form (116). The patient was administered methylprednisolone 500 mg intravenously daily for 2 days, then 250 mg for 3 days, followed by prednisone 25 mg orally for 2 days, and then tapered over 8 days. Verapamil was increased gradually up to 680 mg daily with a subsequent disappearance of attacks. After several months, verapamil was reduced to 320 mg daily without a recurrence of attacks. The same results were achieved in a cohort of 25 patients.

Drs Giorgio Zanchin and Federico Mainardi, Italy

Hypothalamic stimulation for drug-refractory chronic cluster headache (dr-CCH) was started after increased blood flow in the posterior hypothalamus was shown in positron emission tomography studies during cluster headache attacks (117). The first hypothalamic implantation was successfully performed in 2000 in a severe dr-CCH patient (87). So far, more than 90 patients with dr-CCH have been reported in the literature (118–132), including other types of trigeminal autonomic cephalalgia (133–137) with long-term follow-up and good results: pain-free patients or those with ≥ 50% improvement are > 70%. These results are sustained over years (138). More recently, occipital nerve stimulation has been tried. In addition to having less safety concerns, the efficacy figures are similar to deep brain stimulation (139).

In order to improve the efficacy rate and because of the invasiveness of the procedures, the patients must be highly selected by expert headache specialists and thoroughly evaluated by an experienced multidisciplinary team (140).

Dr Massimo Leone, Dr Giovanni Broggi, Dr Gennaro Bussone, Dr Proietti Cecchini Alberto, Dr Giuseppe Messina, Dr Angelo Franzini, Italy

33

Nummular headache

Juan A. Pareja and Carrie E. Robertson

Introduction

Nummular headache (NH) is a well-defined clinical picture characterized by focal head pain exclusively felt in one small, well-circumscribed, area of the surface of the head, in the absence of an underlying lesion.

The term 'nummular' was inspired by the Latin word *nummus*, which means coin (i.e. 'coin-shaped cephalalgia'). NH was described by Pareja et al. in 2002 (1), and in 2018 it was included in the third edition of the International Classification of Headache disorders (ICHD-3) (2).

Since the early description, many other cases have—in a crescendo fashion—increasingly been reported from several countries in Europe, America, and Asia. The worldwide experience with NH is rather impressive, with almost 300 patients with NH reported thus far. It should therefore be possible at this stage to accurately delineate NH clinically.

Epidemiology

Epidemiological data on NH are still lacking. In two hospital-based series, incidences of 6.4/100,000 (3) and 9/100,000 (4) were estimated. In an outpatient neurological service NH represented 0.25% of all consultations, and 1.25% of the consultations for headache (5). In a recent prospective study of patients with unilateral headache, 6% were found to have NH (6).

NH slightly prevails in females (female-to-male ratio 1.5:1), and the mean age of onset is about 44 years (range 4–79 years). The duration of symptoms before diagnosis ranges from < 1 month to 50 years (7,8).

Clinical picture

The most distinctive feature of NH is the topography of the symptoms. The pain is exclusively felt in one small, rounded (80%) or elliptical (20%) area of the surface of the head, with well-defined borders, typically 1–6 cm in diameter (mean 3.5 cm; total range 0.6–10 cm) (7,8).

In most cases of NH the pain is strictly unilateral, with the right side being slightly more affected than the left (7,8). Although any region of the head may be involved, the parietal area, particularly the most convex part (*tuber parietale*), is the common location of NH. Other symptomatic areas include occipital, temporal, frontal, vertex, or crossover regions. Some patients may report a sagittal location (in vertex or occiput) with the symptomatic area divided in half by the midline (3,7–16). Rarely, the disorder may be bifocal or multifocal, with each symptomatic area retaining all the characteristics of NH (7,17–21). The various symptomatic areas may appear simultaneously or dyssynchronously.

The pain is commonly described as oppressive or stabbing, and less frequently as throbbing, sharp, burning, or pulsatile. Pain intensity is generally mild to moderate, but occasionally severe (3,4,13,15,18,22–28). Superimposed on the background pain, spontaneous or triggered exacerbations (lasting from seconds to hours) may occur (1,3,7,9,13–17,25–34). Mechanical stimuli (such as touching or combing hair) on the symptomatic area commonly trigger or exacerbate the pain. Exceptional cases have been reported with the pain possibly precipitated by intercourse (n = 1), coughing and Valsalva manoeuvres (n = 2) (35), menstruation, or sleep deprivation (n = 1) (36).

The affected area frequently shows variable combinations of hypoaesthesia, paraesthesia, dysaesthesia, allodynia, and/or tenderness (1,3). In addition, a minority of patients may develop trophic changes such as a patch of skin depression, hair loss, reddish colour, and local increased temperature (19,25,37). Development of NH in a congenital patch of hair heterochromia has been reported in a 4-year-old child (38). We have also observed emergence of NH in a small area of aplasia cutis.

Autonomic accompaniments are virtually always lacking. Nevertheless, one patient reported bilateral lacrimation and rhinorrhoea during exacerbations (13), and phonophobia has been described in two patients (23,38).

The pain predominates during the daytime and hardly ever awakens patients (3,23,29). The temporal pattern is highly variable: in up to two-thirds of published cases, the disorder has been chronic (present for > 3 months), whereas one-third displayed an episodic pattern with durations of seconds, minutes, hours, or days. During symptomatic days the pain may be continuous, fluctuating,

or intermittent. Rarely, the chronic course evolves from an episodic pattern (3). Spontaneous remissions—with/without recurrence—can ensue (3,39). Persistent remissions after successful treatment have also been described (22,34,40). Pseudo-remissions may be observed when the pain reaches a very low grade or only discomfort (not pain) is reported (39).

Physical examination is normal in the vast majority of cases. Physical examination should include a careful inspection and palpation of the scalp, assessment of tenderness on the emergence and trajectory of all pericranial nerves, and palpation of occipital, temporal, and frontal arteries. Supplementary examinations with analytical (routine blood work, erythrocyte sedimentation rate, standard biochemical determinations, thyroid function) and conventional immunological scrutiny generally render normal results. Neuroimaging studies (such as skull X-ray, computed tomography scan, or magnetic resonance imaging of the head) are commonly normal. Skin biopsies were performed in three patients with trophic changes, and were not specific for any particular dermatological disease (25).

Past history (and temporally related illnesses)

There does not seem to be any tendency towards systematic appearance of any particular antecedents. So far, none of the patients with NH reported has had a family history of circumscribed headache identifiable as NH.

The onset of symptoms is generally spontaneous. Some type of head trauma has been reported in 4–12.8% of patients (8,41,42); however, most of the traumatic incidences were remote, and it is difficult to know whether there was any relationship with the onset of NH (1,3,5,13,16,22,25,40). Only a minority of patients have reported a link between the trauma site and the area where the pain was experienced (3). One patient, for instance, related onset of symptoms after an insect bite in the affected region (25). Another patient developed NH after surgical treatment of a hypophyseal adenoma but in the opposite hemicranium (32).

NH may rarely co-exist with other primary headaches, such as migraine, tension-type headache, medication overuse headache, chronic daily headache, orgasmic headache, primary stabbing headache, epicrania fugax, and trigeminal neuralgia. The onset and course of concurrent headaches have proven to be independent (1,3,7,8,16).

Pathophysiology

Experiments designed to determine the extent and distribution of pain-sensitive structures within the cranium (43,44) have shown that stimulation of the scalp produces sharply localized pain at the site of the stimulus, whereas stimulation of other intracranial structures results in referred pain in a rather wide area.

Clinically, superficial pain is often reported as well localized in a small area. This is consistent with the NH patient's accurate description of their symptoms (Figure 33.1), even outlining the symptomatic area or drawing it in a 1:1 scale. There is generally a good concordance between patient's description and physician's mapping of the symptomatic area (3).

The natural inference from experimental and clinical data is that NH stems from peripheral tissues. The confinement of pain and sensory symptoms to a small cranial area apparently reflects a non-generalized and rather limited disorder. In fact, tenderness and mechanical pain sensitivity (lower pressure pain thresholds) are also restricted to the symptomatic area (Figure 33.2) (45–47). On the contrary, central pain generates symptoms in wider areas, with

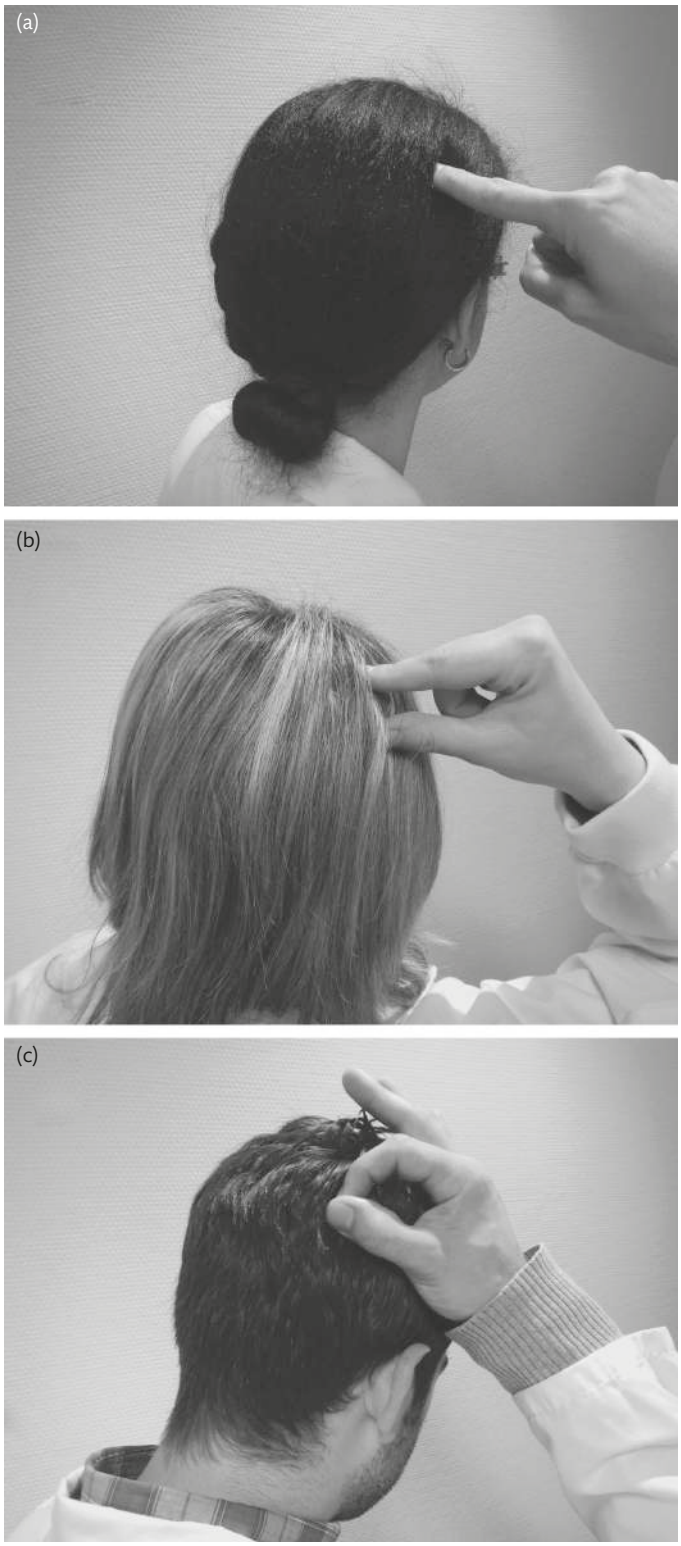

Figure 33.1 Topography of nummular headache (NH).
Patients with NH outlining the symptomatic area: (a) 'Here', (b) 'precisely here', and (c) 'nowhere else but here'.

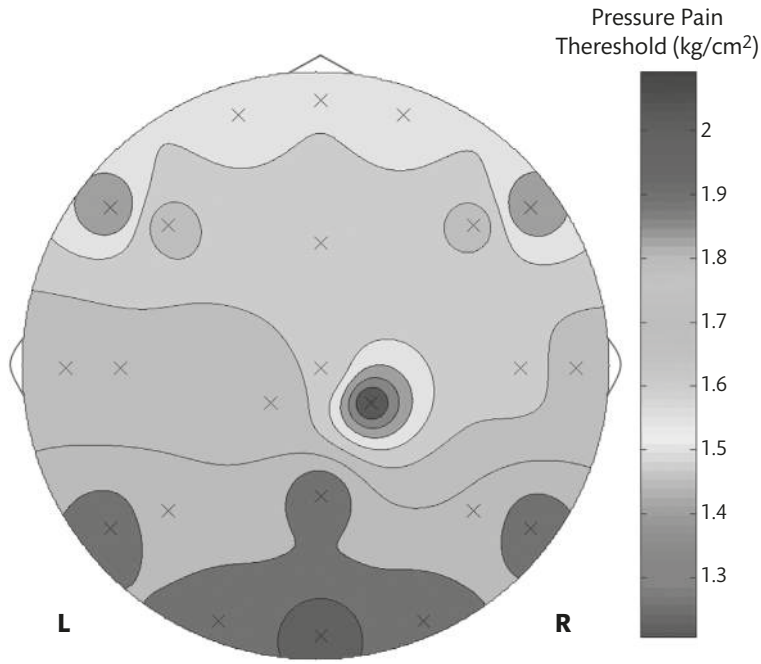

Figure 33.2 (see Colour Plate section) Pressure pain threshold (PPT) topographical map of a patient with nummular headache.

The PPT map shows local hypersensitivity just in the symptomatic area.

L, left; R, right.

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blurred borders, and tends to spread over time (48). NH can be conceived as an in situ headache. The peripheral hypothesis seems to be substantiated by a report (8) of a patient with NH who experienced complete relief after surgical removal of the symptomatic area, although the patient had recurrent NH in a nearby location later.

The size and shape of the symptomatic area, along with signs and symptoms of local sensory dysfunction, suggest neuralgia of a terminal branch of a pericranial nerve. Moreover, trophic changes together with pain and sensory disturbances strongly suggest a lesion or dysfunction of the peripheral nervous system. Specifically, NH with trophic changes (25) might be considered a restricted form of complex regional pain syndrome, which would probably be related to nerve injury. However, two features militate against the neuralgia/neuropathy pathogenesis: (i) anaesthetic block of the symptomatic area is usually ineffective; (ii) the extension of the painful area across the midline (with the symptomatic area divided in half by the midline).

Admittedly, a peripheral pain mechanism is non-existent for headaches attributed to psychiatric disorders as psychogenic headaches should materialize clinically from a central drive. However, some patients with NH may have been dismissed as having neurotic or psychogenic symptoms (12). Neither the clinical features nor psychiatric examinations have pointed to psychological disturbances in NH (1,3,9). It has been documented that NH is not associated with depression or anxiety (49).

As the source of NH is unclear, we prefer to provisionally consider NH as an epicrania, i.e. a headache probably stemming from epicranial tissues—i.e.internal and external layers of the skull, and all the layers of the scalp, including epicranial nerves and arteries (50). This proposal takes into account the possible anatomical source of the pain and may provide interesting clues for research.

Aetiology: primary and secondary cases

The aetiology and pathogenesis of NH are largely unknown, so NH is considered a primary headache (2).

The vast majority of patients with NH have had normal immunological screening. However, one study (51) shows a high prevalence of abnormal autoimmune markers and comorbid disorders in patients with NH. This suggests a possible relationship between NH and autoimmunity, possibly as an autoimmune neuropathy.

Secondary cases have also been described, most typically associated with superficial structural lesions, i.e. arising from the meninges, the skull, or the scalp, and so substantiating the concept of an epicranial pathogenesis (50). Various headaches with a nummular pattern have been related to local lesions of the scalp (fusiform aneurysm of a branch of the superficial temporal artery) (52,53), the skull (fibrous dysplasia) (32), a localized calcific haematoma of the scalp (54), linear scleroderma (55), craniosynostosis (56), or the adjacent intracranial structures (meningiomas, arachnoid cysts) (15,35,57). Such findings make neuroimaging examination of the head a mandatory part of the diagnostic work-up. Concurrency of NH with any other disorder may likely occur just by chance. Additional data, such as complete resolution of the symptoms after surgical/medical treatment of any structural lesion/disturbance, may be needed to fortify the presumption of a symptomatic case.

The periosteum is the pain-sensitive structure of the diploe. The internal periosteum of the diploe is replaced by the endosteal layer of the dura mater. So, we postulate that intracranial processes irritating the endosteal dura may still fit with the concept of epicrania and might theoretically produce a circumscribed pain referred superficially.

Diagnosis

After ruling out secondary aetiologies, diagnosis of NH is based on the clinical features and distinction from other similar headaches (Box 33.1). NH should be considered when encountering other primary headaches and cranial neuralgias with focal symptoms. Within such a clinical frame the possibilities are limited and mainly consist of epicrania fugax, primary stabbing headache, and cranial neuralgias.

Epicrania fugax is a paroxysmal head pain lasting 1–10 seconds, felt in motion from the onset to end, described as a linear or zig-zag trajectory across the surface of one hemicranium, starting and ending in territories of different nerves (58). The stemming area may remain tender in between attacks and this may pose some difficulty in its differentiation from NH. Nevertheless, NH pain is typically continuous and locked in a small cranial area. Superimposed paroxysms do exist in NH, but they always conclude in situ (1,3,58,59). Concurrency of NH and epicrania fugax has been observed (60).

Unlike NH, primary stabbing headache paroxysms are ultra-short (typically 1–3 seconds), multilocalized, and multidirectional (61,62), the attacks changing from one area to another, in either the same or the opposite hemicranium (see also Chapter 23). Occasionally, a short series of primary stabbing headache is side-locked, but then may change side or locations with the next series. In those cases, duration of pain is a helpful distinguishing characteristic.

Neuralgias are defined according to the topography of the pain, which should be perceived within the territory supplied by a given nerve, and can be temporarily inhibited by anaesthetic block of the nerve. None of the acknowledged neuralgias of the head (first branch trigeminal, supraorbital, auriculotemporal, and occipital) had the spatial characteristics of NH (see also Chapter 27) (2,63–65).

Treatment

Owing to the typically moderate severity of the symptoms and benign course, reassurance is adequate in many cases. In patients with low-to-moderate pain, regular analgesics, and non-steroidal anti-inflammatory drugs (NSAIDs) may suffice. In cases with persistent, moderate-to-intense pain, and lack of response to analgesics and NSAIDs, a preventive therapy with neuromodulators may be indicated. In such instances, gabapentin proved to be effective in a substantial number of patients (10,22,40). Alternatively, tricyclic antidepressants rendered satisfactory results in a small series of patients with NH (30). Individual cases have also been reported to respond to topiramate (16,18), carbamazepine (16,66), and indomethacin (34).

Twenty-five units of botulinum toxin type A injected in several points distributed in both the symptomatic and surrounding areas (31), or 10 units injected in the symptomatic area (67), has been tried in 24 cases (18,28,31,68), with a generally good response.

Treatment with transcutaneous electrical nerve stimulation has been reported as effective in one patient with NH (27).

Neurotropin® (a non-protein extract from the inflamed skin of rabbits inoculated with *Vaccinia virus*) has been reported as a useful treatment in three patients with NH (69).

It is worth mentioning that anaesthetic block of the symptomatic area has been tried extensively and was generally of no avail.

Box 33.1 International Headache Society diagnostic criteria for nummular headache

- **A** Continuous or intermittent head pain fulfilling criterion B.
- **B** Felt exclusively in an area of the scalp, with all of the following four characteristics:
  - **1** Sharply contoured
  - **2** Fixed in size and shape
  - **3** Round or elliptical
  - **4** 1–6 cm in diameter.
- **C** Not better accounted for by another ICHD-3 diagnosis.

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Prognosis

NH is a benign condition that may spontaneously remit after a variable duration of symptoms. However, the disorder may last for decades. The few cases in which a clinical picture similar to NH was attributed to a cranial structural lesion proved to have benign underlying conditions with favourable outcome after surgical treatment.

Conclusions

NH is a primary disorder with a clear-cut clinical picture and a distinctive topography. The inherent attribute of NH is that pain and other signs and symptoms of sensory dysfunction always remain in situ—within a small, sharply contoured, symptomatic area that remains immutable over time.

The particular topography and features suggest a peripheral mechanism, particularly a neuralgia of a terminal branch of cutaneous nerves of the scalp, although it has not yet been demonstrated. A provisional concept of epicrania has been proposed to group NH and other headaches with a probable source in the epicranial tissues.

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PART 6

Secondary headaches

Diagnosis and treatment

34. **Thunderclap headache** *307*
Hille Koppen, Agnes van Sonderen, and Sebastiaan F. T. M. de Bruijn

35. **Headache associated with head trauma** *314*
Sylvia Lucas

36. **Cervicogenic headache** *322*
Nikolai Bogduk

37. **Headache and neurovascular disorders** *334*
Marieke J.H. Wermer, Hendrikus J. A. van Os, and David W. Dodick

38. **Headache attributed to spontaneous intracranial hypotension** *346*
Farnaz Amoozegar, Esma Dilli, Rashmi B. Halker, and Amaal J. Starling

39. **Headache associated with high cerebrospinal fluid pressure** *356*
Ore-ofe O. Adesina, Sudama Reddi, Deborah I. Friedman, and Kathleen Digre

40. **Headache associated with systemic infection, intoxication, or metabolic derangement** *367*
Ana Marissa Lagman-Bartolome and Jonathan P. Gladstone

41. **Headache associated with intracranial infection** *384*
Matthijs C. Brouwer and Jonathan P. Gladstone

42. **Remote causes of ocular pain** *392*
Deborah I. Friedman

43. **Orofacial pain: dental head pains, temporomandibular disorders, and headache** *399*
Steven B. Graff-Radford† and Alan C. Newman

44. **Headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL) syndrome** *403*
Germán Morís and Julio Pascual

45. **Nasal and sinus headaches** *409*
Vincent T. Martin and Maurice Vincent

46. **Giant cell arteritis and primary central nervous system vasculitis as causes of headache** *418*
Mamoru Shibata, Norihiro Suzuki, and Gene Hunder

47. **Headache related to an intracranial neoplasm** *428*
Elizabeth Leroux and Catherine Maurice

48. **Headache and Chiari malformation** *442*
Dagny Holle and Julio Pascual

49. **Reversible cerebral vasoconstriction syndromes** *447*
Aneesh B. Singhal

34

Thunderclap headache

Hille Koppen, Agnes van Sonderen, and Sebastiaan F.T.M. de Bruijn

Introduction

Thunderclap headache refers to the abrupt onset of a severe headache (1–3). The characteristics of the pain are not strictly defined, but intensity is considered to peak within 1 minute. The International Classification of Headache Disorders (ICHD) gives criteria for primary thunderclap headache: namely, maximal intensity within 1 minute and a duration of at least 5 minutes (4). Some studies include patients with headache reaching maximum intensity in up to 1 hour. Patients often describe 'the worst headache ever', which refers to the intensity of the pain, and not its abrupt onset. The differential diagnosis of thunderclap headache is extensive, and the diagnosis of primary thunderclap headache can only be made once secondary causes have been excluded. The initial work-up is focused on detecting or excluding a subarachnoid haemorrhage (SAH), after which other secondary causes of thunderclap headache should be considered, such as reversible cerebral vasoconstriction syndrome (RCVS), cervical artery dissection, cerebral venous sinus thrombosis (CVST), and stroke (see Table 34.1). This chapter focuses on the work-up of alert neurologically intact patients presenting with an acute and severe headache, not related to trauma. Work-up to detect or exclude a SAH is described first, followed by an overview of investigations to detect a cerebral aneurysm (see Figure 34.1). Thereafter, other secondary causes of thunderclap headache and their suitable analysis will be discussed, followed by a brief overview of primary thunderclap headaches.

Subarachnoid haemorrhage

Epidemiology

The prevalence of SAH among alert and neurologically intact patients with thunderclap headache probably is around 10% (6). The incidence of SAH is estimated at nine cases per 100,000 person-years, accounting for approximately 5% of all strokes (7). Half of the SAHs occur in patients younger than 55 years of age. An aneurysm is found in approximately 85% of the SAHs (8). About 10% of the SAHs is non-aneurysmal, mostly showing a perimesencephalic blood configuration. However, a posterior circulation aneurysm is found in approximately 9% of the patients with a perimesencephalic blood distribution on head computed tomography (CT) (9). Another 5% of SAHs are due to rare causes such as spinal arteriovenous malformations or arteritis (8).

Clinical features

There are no clinical features to distinguish headache due to a SAH from other causes of thunderclap headache. In a series of 42 patients with aneurysmal SAH headache evolved within a minute in 75% of patients. Headache usually lasts for 1–2 weeks, but the exact limits of duration are unknown, including the shortest duration. Besides abrupt onset of severe pain in the head, patients may experience nausea, vomiting, photophobia, neck stiffness, seizures, and brief loss of consciousness. (6,10).

Only some of the patients with an aneurysmal SAH retrospectively report a sudden and severe headache in the 4 weeks prior to the SAH. This can be due to either enlargement of the aneurysm causing 'sentinel headache', or due to an undiagnosed minor SAH (sometimes referred to as a 'warning leak', but this is a true SAH) (6). The significance of these phenomena is unknown, mainly owing to the retrospective nature of the obtained information.

Diagnostic work-up: detecting or excluding a SAH

Timely detection of an aneurysmal SAH is essential because of the high risk of a re-bleed (8,11). Early treatment to prevent a re-bleed is related to better outcome, which underlines the need for immediate diagnosis (12).

Head CT

The initial investigation in all patients suspected of having a SAH is a head CT. Accuracy is influenced by the amount of subarachnoid blood and the interval between the onset of symptoms and the time of scanning. As time passes, blood will spread away from the bleeding site, and haemolysis will impede the detection of blood on CT within hours. Blood in the subarachnoid space is visible on CT as an increased attenuation of the basal cisterns and subarachnoid spaces. In perimesencephalic SAHs, blood is confined to the cisterns around the midbrain, with possibly limited extension of blood to the interhemispheric and Sylvian fissure.

Table 34.1 Causes of thunderclap headache.

Thunderclap headache in secondary headaches (4)	Thunderclap headache in primary headaches
More common causes • Subarachnoid haemorrhage (8) • Reversible cerebral vasoconstriction syndrome (39,41) • Cervical artery dissection (45–47) • Cerebral venous sinus thrombosis (48–51) • Spontaneous intracranial hypotension (52–54) • Stroke (ischaemic, haemorrhagic) (56–60) • Pituitary apoplexy (61–63)	• Primary cough headache (4) • Primary headache associated with sexual activity (4) • Primary thunderclap headache (4) • Primary exercise headache (4)
Miscellaneous causes • Retroclival haematoma (64,65) • Meningitis or vasculitis (59) • Acute hydrocephalus (aqueduct stenosis (67)/colloid cyst (68) • Sinusitis (66) • Cardiac cephalalgia (70,71) • Phaeochromocytoma (69)	

In the past, the sensitivity of unenhanced head CT for the detection of a SAH was reported to be between 90% and 98%. Two studies report a sensitivity of 100% if CT is performed within 6 hours after headache onset. The first report is a prospective study from 2011, which investigated 3132 alert patients without focal neurological deficits, with headache peaking in intensity within 1 hour. In patients with a negative head CT, a SAH was ruled out by either lumbar puncture or a 6-month follow-up. Overall sensitivity of CT scan was 92.9% (95% confidence interval (CI) 89.0–95.5). In the subgroup of 669 patients with head CT performed within 6 hours after ictus, 67 patients showed a SAH on CT. In the CT-negative patients, no SAH was diagnosed by lumbar puncture or during follow-up, resulting in a sensitivity of 100% for head CT within 6 hours after ictus. The sensitivity for head CT performed more than 6 hours after ictus was 85.7% (95% CI 78.3–90.9). The study has some methodological limitations. The number of patients who did not have a lumbar puncture after a negative CT was not reported. In these patients, a SAH could have be missed if no re-bleed had occurred within the next 6 months. Besides, if a lumbar puncture was performed, cerebrospinal fluid (CSF) analysis consisted of visual xanthochromia or red blood cells (RBCs) in the final tube, which might not be the most accurate methods in detecting subarachnoid blood, as stated later on (13). A second study was published in 2012 and had a retrospective design. Two hundred and fifty patients were included, all suspected of having a SAH, with a maximum Glasgow Coma Scale score and no focal neurological deficits. Of the 137 patients who had a CT performed within 6 hours after ictus, a SAH was visible in 68. The remaining 69 patients had a lumbar puncture. CSF was analysed using absorption spectrophotometry. CSF analysis was positive for bilirubin in only one patient. This patient had presented with neck pain and stiffness without headache, and appeared to have bled from a cervical arteriovenous malformation. The sensitivity of CT cerebrum within 1 hour was 98.5% (95% CI 92.1–100), including this patient. If only patients presenting with acute headache were included in the analysis, the sensitivity increased to 100% (95% CI 94.6–100). This study showed a sensitivity of 92.3% (95% CI 79.1–98.4) for CT performed after 6 hours (but within 10 days after ictus) (14).

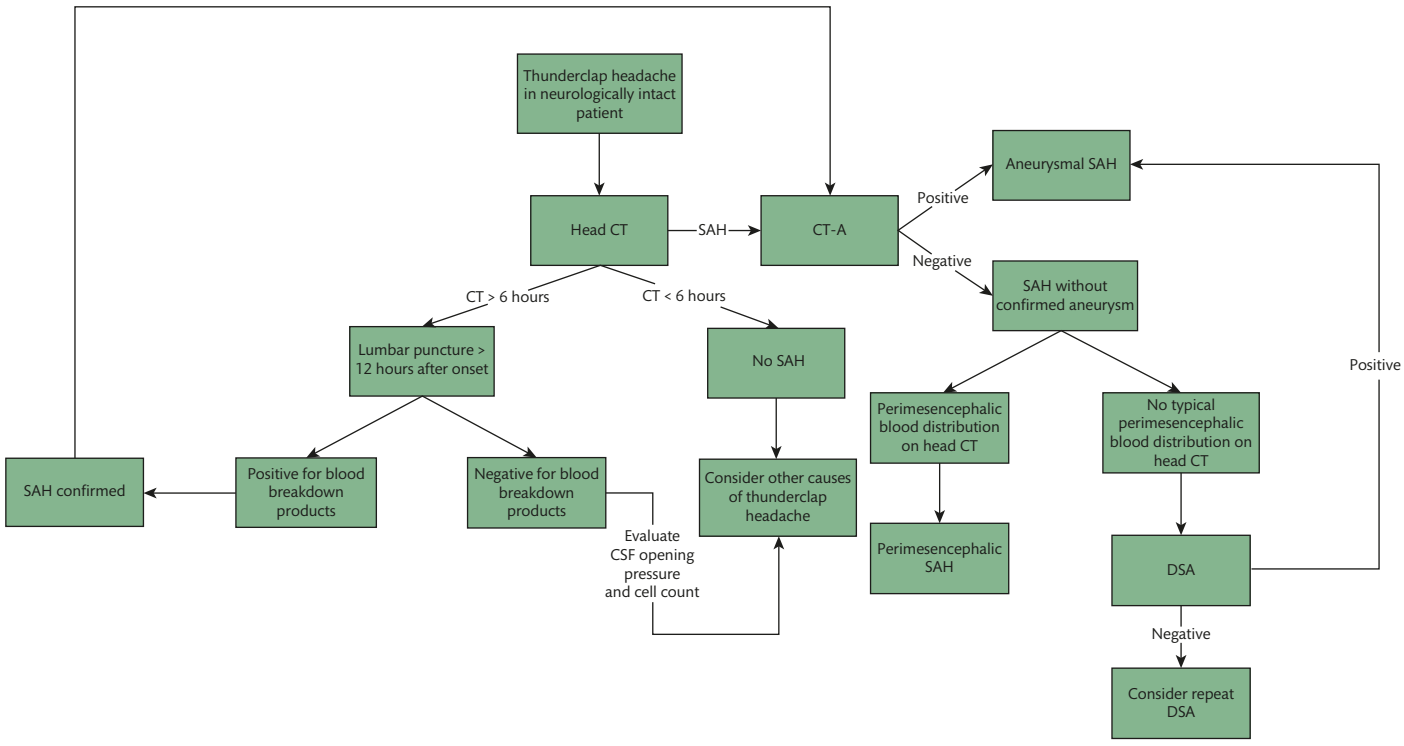

Figure 34.1 Diagnostic evaluation of neurologically intact patients with thunderclap headache.
CT, computed tomography; CT-A, computed tomographic angiography; SAH, subarachnoid haemorrhage; CSF, cerebrospinal fluid; DSA, digital substraction angiography.

In conclusion, in patients presenting with acute headache with a normal level of consciousness and no focal neurological deficit, a normal head CT performed within 6 hours is sufficient to exclude a SAH. Evidence is based on studies in which CT scans were interpreted by a qualified (neuro-)radiologist. In patients presenting more than 6 hours after ictus, a negative CT is insufficient to rule out a SAH. In these cases, CSF analysis in indicated, preferably by means of spectrophotometry.

False-positive CT results can be seen as a result of radiological SAH mimics, also called pseudo-SAHs. This mostly applies to patients with raised intracranial pressure, such as cases of cerebral oedema or bacterial meningitis. The increased intracranial pressure forces CSF out of the subarachnoid space. Meanwhile, engorgement of venous structures causes increased attenuation of the subarachnoid space on CT, mimicking a SAH. Additionally, the attenuation of the brain parenchyma decreases as a result of brain swelling. Leakage of intravenous contrast into the subarachnoid space is another potential SAH mimic on CT (15,16). False-positive CT results can be harmful to the patient due to redundant invasive examinations, and because it moves the focus away from other secondary causes of thunderclap headache.

Lumbar puncture and CSF analysis

Blood in the subarachnoid space can be detected by CSF analysis. Therefore, a lumbar puncture is the next step in excluding or identifying a SAH, unless a SAH is sufficiently excluded by head CT within 6 hours. In patients with a negative head CT done 6 hours or more after ictus, approximately 5% turn out to have a SAH, following positive CSF analysis (14). It is also recommended that CSF opening pressure is measured as well. Although not contributing to identifying a SAH, CSF pressure can be helpful in analysing other secondary causes of thunderclap headache such as cerebral venous thrombosis, once a SAH is excluded.

Methods for CSF analysis

Three methods of CSF analysis for the diagnosis of a SAH are in use, namely RBC count and the detection of breakdown products by xanthochromia and spectrophotometry. In our opinion, the latter is thought to be most reliable, but there are no studies available comparing these three methods, and local preferences differ. The mainstay of CSF analysis in the UK is spectrophotometry, whereas visual inspection and RBC count is more widely used in the USA (17). In all three methods, the distinction between a SAH and a traumatic puncture can be challenging. Waiting to perform lumbar puncture at least 12 hours after ictus may be of great value. False-positive results can be harmful to the patient because of subsequent unnecessary cerebral angiography, while a false-negative outcome results in the risk of a re-bleed in an untreated aneurysm.

The reported method of analysing CSF within 30–60 minutes after ictus is RBC count in the CSF but should be avoided. RBCs also emerge into the CSF in the case of a traumatic tap. A decrease in the number of RBCs in successive tubes is said to indicate a traumatic puncture, but if a patients does, indeed, have a SAH and a traumatic puncture is performed, the number of RBCs will decrease in successive tubes anyway. The conclusion that a SAH is ruled out would be incorrect. Additionally, there is no defined threshold for the number of RBCs in the CSF indicating a SAH.

Analysis of blood breakdown products is considered most reliable in making a distinction between a SAH and a traumatic puncture. Breakdown products can be detected within 12 hours after ictus and remain detectable for at least 2 weeks (18). Haemolysis of erythrocytes after a SAH leads to the release of oxyhaemoglobin in the CSF. Through enzymatic reactions, oxyhaemoglobin is further degraded to bilirubin by macrophages, which occurs in vivo only. In CSF tapped after 12 hours of the ictus, oxyhaemoglobin can still be the result of a traumatic puncture, but bilirubin indicates an earlier haemorrhage (17,19). There are two exceptions: bilirubin is also detectable in the CSF in case of serum hyperbilirubinaemia, or when CSF bilirubin is raised as a result of a high CSF albumin, to which bilirubin binds. The combination of pre-existing CSF bilirubin and oxyhaemoglobin due to a traumatic puncture can be misleading. Therefore, to rule out a false-positive result, serum bilirubin concentration and CSF protein level should be measured if CSF analysis is positive (20). Tapped CSF should not be exposed to light because light increases the rate of bilirubin degradation.

Once a puncture is performed 12 hours after the ictus, there are two methods with which to detect bilirubin in the CSF. The most basic method is visual evaluation of CSF, based on the yellowish discolouration of CSF containing bilirubin, called xanthochromia. The sensitivity of this procedure is limited because human colour vision is insufficient to detect small amounts of bilirubin and it is difficult to differentiate the colours of haemoglobin and bilirubin (17,21,22). CSF pigments can be analysed more reliably with spectrophotometry, in which the absorption spectrum is measured for several haeme pigments in the CSF (17,23). This requires special equipment and understanding of the time course of development of haeme pigments.

A lumbar puncture is frequently complicated by post-lumbar puncture headache. More hazardous complications, such as infections and subdural haematoma, are rare.

Negative head CT and negative CSF analysis

There are a few case reports of patients with a negative head CT and lumbar puncture who appeared to have an aneurysm (24). However, asymptomatic aneurysms are reported in about 2–3% of the population (25,26). The yield of searching for, and possibly treating of, an unruptured aneurysm is unclear. Besides, prospective studies do not support the need for angiography in patients with negative head CT and negative CSF analysis (27). The chance of detecting an asymptomatic aneurysm, the potential risks related to invasive examinations, patient discomfort, and the cost of further examination and extended hospital admission should be balanced against the slight risk of missing a SAH if analysis is terminated as this point.

SAH confirmed: aneurysm detection

Once a SAH is diagnosed, further investigation is focused on the detection of an aneurysm, which is found in approximately 85% of cases (8). Although intra-arterial digital subtraction angiography (DSA) is the gold standard, CT angiography (CTA) is currently the most feasible investigation to start with. CTA is non-invasive, readily available in the emergency setting, and it can be performed immediately after blood is detected on unenhanced CT. In most cases, CTA is also accurate in determining feasibility for coiling. Therefore, the decision between open neurosurgical clipping and endovascular

management can be made within a short time. The sensitivity of CTA in detecting cerebral aneurysms was investigated in a meta-analysis. Forty-five studies were included, comprising 3643 patients, of whom 86% were investigated because of a non-traumatic SAH. The sensitivity of CTA in detecting an aneurysm in a patient was 97.2% (95% CI 95.8–98.2), specificity was calculated to be 97.9% (95% CI 95.7–99.0), with DSA as the reference standard. Higher-class CT containing 16 or 64 detector rows is more sensitive, which is especially meaningful in the detection of smaller-sized aneurysms (< 4 mm) (28). DSA is currently not the examination of first choice because it is a time-consuming and invasive procedure, with potential risks of complications: groin haematomas occur in 4.2% of patients, stroke with permanent deficit is seen in 0.14% of cases, and death occurs in 0.06%. An increased risk of neurological complications is seen in patients investigated because of a SAH (29). The advantage of DSA is the opportunity to perform endovascular coiling at once, whenever this seems feasible. An alternative for CTA or DSA is magnetic resonance angiography (MRA). MRA is non-invasive and radiation- and contrast-free. Accuracy is good, but feasibility is poor in the setting of a SAH, owing to limited availability in the emergency setting, longer scan time, and patient-specific contraindications to undergo magnetic resonance imaging (MRI) (30,31).

In conclusion, the search for an aneurysm in patients with a confirmed SAH starts with a CTA. If no aneurysm is seen on CTA, and blood distribution is typical for a perimesencephalic haemorrhage, it is reasonable to end the work-up (8,32). In all other cases, a negative CTA should be followed by DSA. The yield of repeat DSA after initial negative CTA and DSA is under debate. There should not be an infinite search for an aneurysm, knowning the significant rate of non-aneurysmal SAHs. However, several cases of aneurysms detected on a second DSA are reported, even after a negative CTA (33–35). In the situation of a lack of consensus, clinician preference and patient characteristics influence to which extent patients are analysed.

Prognosis

The mortality rate of SAHs is high. Ten to fifteen per cent of patients die before reaching the hospital. Additionally, the 30-day case fatality rate is 28.7–36.5% in hospitalized patients (36,37). In untreated aneurysmatic SAHs, the risk of a re-bleed is estimated to be up to 12% in the first 24 hours (11). In patients who survive the first day, the risk of a re-bleed in an untreated aneurysm is approximately 40% in the next 4 weeks. Eighty per cent of the patients who experience a re-bleed die or remain disabled (8). To prevent a re-bleed in aneurysmatic SAHs, the aneurysms can be treated by either endovascular coiling or open neurosurgical clipping. About 10% of SAHs are due to a non-aneurysmal perimesencephalic haemorrhage. Treatment in these patients is supportive, with analgesics and control of blood pressure, and outcomes are excellent (8,38).

Other secondary causes of thunderclap headache

The primary focus in thunderclap headache is directed on detecting or excluding a SAH. Once a SAH is excluded, it is mandatory to exclude a range of conditions, as stated in the ICHD (4). These secondary causes of thunderclap headache are discussed in the following subsections and in Table 34.1.

Reversible cerebral vasoconstriction syndrome

Recurrent attacks of thunderclap headache over a few days are the most common presenting symptom of RCVS (see also Chapter 49). The headache is of severe intensity with a peak within 1 minute (4). Headache can last for minutes up to days, but usually resolves after 1–3 hours. Patients may report nausea, vomiting, photophobia, and phonophobia. Focal neurological deficits are seen in 8–43% of the cases. Patients experience an average of four attacks in 1–4 weeks. A moderate headache can persist between these attacks (39). RCVS can be complicated by focal or generalized seizures. Haemorrhages and ischaemia may cause transient or permanent impairment. Several conditions are known to trigger an attack in RCVS, among which are sexual activity (before of just at orgasm), exertion, Valsalva-like manoeuvres, emotions, bending, bathing, and showering (4). The pathophysiology of RCVS and its time course are not yet fully established. Ducros et al. (40) suggested that alternating vasoconstriction and vasodilatation starts in smaller vessels and progresses towards medium- and large-sized vessels. Thunderclap headache may be triggered by stretching of vessel walls. Early in the course of disease, haemorrhages may be seen as a result of small-vessel rupture or reperfusion injury. After disease progresses to larger vessels, secondary vasoconstriction in these vessels may cause watershed infarction. RCVS is slightly more common in women than in men, with a mean age of onset of 42 years. Several clinical conditions are associated with RCVS. The most common are pregnancy, the postpartum period, exposure to vasoactive medications such as selective serotonin reuptake inhibitors, triptans, and recreational drugs, such as cocaine and cannabis. Any of these conditions is seen in at least half of the cases (4). Other associated conditions are the exposure to blood products, catecholamine-secreting tumours and vascular disorders as unruptured aneurysm and cervical artery dissection (39,41). RCVS seems to occur more frequently in patients having migraine, and migraine patients are prone to evolve the haemorrhagic complications of RCVS.

Fifty-five per cent of patients with RCVS have normal head CT or MRI at initial presentation. Vasoconstrictions may not be observed in the early stages of RCVS. However, most patients evolve abnormalities in the course of the disease (42). Convexity SAH is not only suggestive of RCVS, but can also be seen in amyloid angiopathy, most often seen in the elderly. CT may show parenchymal haemorrhage early in the course of the disease. Cerebral infarction is seen in a minority of patients, mostly occurring in the second week. Brain oedema can be seen as well, with a similar distribution as in posterior reversible encephalopathy syndrome (43). The gold standard for diagnosing the alternating pattern of vasodilation and vasoconstriction seen in RCVS is cerebral angiography. Indirect methods such as CTA and MRA are non-invasive and seem to be a good alternative to show the strings-of-beads pattern. Comparative studies are not available. Because the disease is suspected to affect smaller arteries first, and disease in these arteries is difficult to see, negative vascular examination should be repeated after 1–2 weeks. At that time, vasoconstriction and vasodilatation of middle-sized and large arteries may be seen. Vasculitis may also cause vessel irregularity, but thunderclap headache is less likely in vasculitis. Transcranial Doppler may show vasospasm in RCVS. Abnormalities in blood flow are usually not as severe as seen in patients with an aneurysmal SAH (44). CSF abnormalities occur in a minority of patients with

RCVS and may include a raised protein concentration or raised white blood cell count.

RCVS is a self-limiting condition. Vasoconstriction resolves either partially or completely within 12 weeks. Management of RCVS is based on expert opinion. Patients are recommended to rest for several weeks. Triggers of thunderclap headache such as physical exertion and vasoactive drugs should be avoided. Pain should be controlled by analgesics. Empirical therapies to control vasospasm include nimodipine, verapamil, and magnesium sulfate. Blood pressure should be monitored carefully, aiming for normotension. Hypertension should be treated with caution, considering the risk of watershed infarction related to hypotension.

Cervical artery dissection

Thunderclap headache can be the presenting symptom of a cervical artery dissection. Pain in the head and neck are common features of cervical dissection, often accompanied by other symptoms such as Horner's syndrome, cranial nerve palsies and retinal and cerebral ischemia. It is a major cause of strokes in young adults. Pain in the head is thought to be referred pain. It usually occurs ipsilateral to the dissection, but bilateral pain is reported as well. In vertebral arterial dissection, cervical and occipital pain are frequent. Temporal and frontal pain is reported in cervical artery dissections more often (45,46). An analysis of 1027 patients with a spontaneous cervical artery dissection showed headache in 71.1%. Pain was more intense in vertebral artery dissection than in carotid artery dissection. Thunderclap headache, which was not further specified in this study, was seen more often in vertebral artery dissection. The overall incidence of thunderclap headache was 5.4%. However, a significant number of patients also had a SAH related to the dissection (47).

Cerebral venous sinus thrombosis

CVST presents with headache in 80–90% of cases (see also Chapter 37). Headache is usually accompanied by other symptoms such as focal neurological deficits, altered mental state, or seizures. However, CVST can be seen in patients presenting with a headache as the sole manifestation, even if head CT and CSF pressure are unremarkable (48,49). There is no identifiable uniform pattern of headache in CVST (50). Patient series of CVST have shown thunderclap headache in 2.4–14% of cases (48–51). Some patients are more susceptible to developing a CVST. This applies, in particular, to patients in a hypercoagulability state, such as genetic coagulability disorders, sepsis, and hormone-related hypercoagulability, such as pregnancy, the postpartum period, and the use of oral contraceptives. Structural damage to the sinuses after head trauma is a risk factor as well. MRI is the imaging method of choice to visualize a thrombus, and may also show complications such as oedema, intracerebral haemorrhage, or venous infarction. Imaging of the venous sinuses by MR venography or CT venography is useful to demonstrate the absence of flow in the occluded venous sinuses. In all patients with thunderclap headache analysed with lumbar puncture, opening pressure should be measured. A raised opening pressure (> 250 mm CSF) raises the suspicion on a underlying cause of thunderclap headache, such as CVST. Relief of the headache after CSF tap supports this. However, a raised CSF opening pressure is neither sensitive nor specific for CVST.

Spontaneous intracranial hypotension

In case of spontaneous intracranial hypotension patients experience orthostatic headache, which may be accompanied by neck stiffness, tinnitus, and diplopia (see also Chapter 38). An acute severe headache is reported in 14–16% of patients, although a recent small series showed a higher incidence (52–54). Intracranial hypotension is due to a spinal CSF leak. Characteristic features on head MRI are downward displacement of the brain, diffuse pachymeningeal enhancement, and subdural fluid collections (55). Lumbar puncture is not recommended to diagnose intracranial hypotension, but low CSF pressure can be an incidental finding in the analysis of a patient with headache. Liquor hypotension is defined as a CSF pressure < 60 mm CSF (4).

Stroke

Thunderclap headache as isolated symptom may rarely be the presenting feature of an ischaemic stroke, as described in a few case reports (see also Chapters 10 and 37). Patients had experienced a thunderclap headache, after which neurological examination, head CT, and CSF analysis were normal, but diffusion-weighted MRI showed acute cerebral ischaemia. One of these case reports described normal MRA as well, but in the other reports specific causes of stroke, such as cervical dissection or RCVS, were not excluded (56–58). Patient series of thunderclap headache report cases of parenchymal and intraventricular haemorrhages as well; however, these series do not report whether patients had deficits on neurological examination, suggesting a stroke at presentation (59,60).

Pituitary apoplexy

Pituitary apoplexy was the cause of thunderclap headache in some case reports. Patients present with sudden onset of severe headache, which is followed by nausea, vomiting, visual disturbance, and diplopia in the next few hours to days. The initial presentation can mimic a SAH. Pituitary apoplexy is most often caused by haemorrhage into a macroadenoma of the pituitary gland. Diagnosis can be challenging because pituitary apoplexy is easily missed on head CT (61–63).

Miscellaneous causes of thunderclap headache

A few cases of thunderclap headache are reported in patients with a retroclival haematoma (64,65), meningitis (6,59), sinusitis (66), and aqueduct stenosis (67). Colloid cysts of the third ventricle may present with attacks of abrupt severe headache, resolving abruptly after change of position (68). Recurrent episodes of thunderclap headache are reported in phaeochromocytoma (69). Headache during an episode of cardiac ischaemia, knows as cardiac cephalalgia, rarely presents with a thunderclap headache as the sole manifestation (70,71). Acute glaucoma may present with thunderclap headache as well.

Primary headaches

Primary thunderclap headache refers to high-intensity headache of abrupt onset in the absence of intracranial pathology. The maximum pain intensity should be reached within 1 minute, whereas the pain should last at least 5 minutes. As thunderclap headache is often

caused by serious intracranial disorders, particularly SAH, extensive examination of an underlying cause should be negative (this means normal brain imaging, including the brain vessels, and normal CSF) to make the diagnosis of primary thunderclap headache (4). Cervical vascular imaging should also be considered.

Thunderclap headache can also be related to cough, exercise, or sexual activity (see also Chapters 24 and 25). Primary cough headache arises moments after the cough and reaches maximum intensity immediately. Primary headache associated with sexual activity usually starts as a dull ache as sexual excitement increases and suddenly exacerbates at orgasm. These two types of primary headache may recur with the recurrence of respectively coughing or sexual activity (4). Distinction should be made with RCVS, in which sexual activity is one of the possible triggers for an attack (see also Chapter 49). Some cases of sudden severe headache during weightlifting are reported, fulfilling criteria for primary exercise headache (72).

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35

Headache associated with head trauma

Sylvia Lucas

Introduction

Traumatic brain injury (TBI) has become an extremely important global health issue in the past several years. Considerable attention and interest has focused on several populations susceptible to TBI: soldiers deployed in war zones, professional athletes and young people involved in school sports activity, and civilians engaged in usual activities of daily living who may be involved in motor vehicle accidents, falls, or assaults, among other injuries.

In the USA, approximately 2.5 million civilian TBIs occurring each year present for medical attention. In 2010, The Centers for Disease Control estimated that 87% of those were treated and released from emergency departments (ED), 10% were hospitalized and discharged, and 2% died (1). These numbers do not account for persons with TBI who never receive medical attention or have office-based outpatient visits, or for those receiving care at federal facilities such as in military or Veterans Administration hospital systems. In the USA there is limited information on TBI-related disability, with estimates ranging from 3.2 to 5.3 million persons living with disability 1 year after injury (2).

In the USA, 75% of TBI is classified as mild TBI (mTBI), whereas in a New Zealand cohort, 95% of brain injuries were mTBI (2). The aetiology of mTBI is different in different age groups. For example, falls are the most common cause of mTBI in children aged 0–4 years and in adults over the age of 75 years (1,3). Rates of TBI-related ED visits increased the most for those younger than 4 years of age, who have the highest rate of injury of any age group, with almost twice the rate of those in the next highest age group (15–24 year olds). Although rates of TBI have increased, particularly in men, civilian deaths have declined in the past decade, likely from industry improvements in air bag technology for vehicle occupants and seat belt requirements in motor vehicles, protective helmet design for use in sports activities and two or three-wheeled vehicle use, and other public health-driven protective measures.

Sports-related head injuries, almost always resulting from mTBI, may be underestimated for reasons other than not seeking care by medical professionals or others who could report injury rates. Many athletes, especially younger players, may not recognize symptoms of concussion or head injury; others may minimize their injury or will not report an injury because of a strong desire to remain in the game. The incidence of sports-related concussion has been estimated at 3.8 million events per year in a population of 44 million children and 170 million adults in organized sports activity participation (4).

The most common aetiology of the additional TBI burden in military or civilian personnel in active military missions in Iraq, Syria, or Afghanistan is exposure to combat-related explosions with approximately 80% of mTBI secondary to blast exposure (5,6). Injury to military personnel reported by the Congressional Research Service show a total of 327,299 TBI cases between 1 January 2000 and 5 June 2015 with 269,580 mild, 27,728 moderate, 8,287 penetrating or severe, and 21,704 not classifiable (7).

Post-concussive symptoms

Concussion is a symptom manifestation of a TBI, but the term 'concussion' and mTBI are not synonymous. Headache is the most common physical symptom following TBI; however, it may not occur in isolation. Headache may be part of a symptom complex known as the post-concussion syndrome (PCS) comprising physical or somatic, psychological, and cognitive symptoms (8,9). One prospective, longitudinal study of symptoms following 1 month after TBI reported the most common symptoms as fatigue, headache, dizziness, memory trouble, trouble sleeping, trouble concentrating, irritability, blurred vision, anxiety, increased light, and sound sensitivity (10). Severity of brain injury was correlated with number of symptoms and more severe injuries tended to be associated with a greater proportion of cognitive and psychological symptoms in addition to physical symptoms. Studies of sports concussions report that females have higher rates of concussion and have greater post-concussion cognitive changes (4,11). When comparing the same sports, such as softball/baseball, girls have almost twice the rate of concussion than boys (12,13), which may be from biomechanical (e.g. smaller head/neck mass or head-to-ball mass ratios, or weaker neck muscles) (11), or sociological factors, or both.

Post-traumatic headache

Posttraumatic headache (PTH) has no defining clinical features, and is classified as a secondary headache disorder in the International

Classification of Headache Disorders, third edition (ICHD-3) (Box 35.1) (14). A secondary headache is a headache that occurs in close temporal relation to another disorder that is presumed to cause the headache, or fulfils other criteria for causation by that disorder; the new headache is coded as a secondary headache attributed to the causative disorder. Secondary headaches may have characteristics of primary headaches (migraine, tension-type headache, cluster headache, or one of the other primary headaches). This may be problematic in persons who have pre-existing primary headache disorders. If the headaches are worsened in frequency or intensity in close temporal relationship to the presumptive causative injury, then the new or worse headaches are defined as PTH.

Primary headache disorders are described and classified on the basis of clinical symptoms and are thought to be genetically acquired syndromes that involve trigeminovascular pathway dysfunction. Although the physiology of the primary headache disorders is not clear, animal models of neurogenic inflammation and cortical spreading depression (CSD), limited human imaging studies, and the response of migraine to a class of drugs known as 'triptans' (e.g. sumatriptan), which act as agonists at serotonin (5-HT) 1B/1D receptors, give us potential physiological pathways of head pain (15). PTH, as a secondary headache, is thought to have a structural or functional causation that, if corrected, would result in the resolution of the secondary headache. To support a temporal relationship between injury and onset of headache, the ICHD requirement that PTH occur within 7 days after an injury does not necessarily ensure causation. Many reports of PTH occurring more than 7 days after an injury have been published. In a prospective study of civilians with moderate-to-severe TBI, approximately 28% of new headaches were reported 3 months after the injury (16). Following mTBI, 32% of hospitalized paediatric patients reported headache 2–3 weeks after the injury (17). In a study of active duty US soldiers, only 27% of headaches were reported to develop within a week of mild head injury (18). If the ICHD classification of PTH is strictly adhered to, up to one-third of PTH could be underdiagnosed on the basis of latency constraints and therefore clinical judgement may be required to make causation.

Post-traumatic headache epidemiology

Despite headache being the most common symptom after TBI, the prevalence has ranged from 30% o 90% in retrospective studies (19–22). Comparison of brain injury studies is difficult because of variability in subject selection, case ascertainment, TBI severity, inclusion and exclusion criteria, and study length. Select epidemiological civilian adult and paediatric, as well as military studies are shown in Table 35.1 (10,16,23–33).

In one civilian prospective study of 452 people admitted to inpatient rehabilitation units after a moderate-to-severe TBI, the majority

Box 35.1 International Classification of Headache Disorders criteria for post-traumatic headache

5.2.1 Acute headache attributed to moderate or severe traumatic injury to the head

Diagnostic criteria:

- **A** Any headache fulfilling criteria C and D.
- **B** Traumatic injury to the head associated with at least one of the following:
  - **1** Loss of consciousness for > 30 minutes
  - **2** Glasgow Coma Scale (GCS) score < 13
  - **3** Post-traumatic amnesia lasting > 24 hours
  - **4** Altered level of awareness for > 24 hours
  - **5** Imaging evidence of traumatic head injury such as intracranial haemorrhage and/or brain contusion.
- **C** Headache is reported to have developed within 7 days after one of the following:
  - **1** The injury to the head.
  - **2** Regaining consciousness following the injury to the head.
  - **3** Discontinuation of medication(s) that impair ability to sense or report headache following the injury to the head.
- **D** Either of the following:
  - **1** Headache has resolved within 3 months after the injury to the head
  - **2** Headache has not yet resolved, but 3 months have not yet passed since the injury to the head.
- **E** Not better accounted for by another ICHD-3 diagnosis.

5.2.1.1 Persistent headache attributed to moderate or severe traumatic injury to the head

Diagnostic criteria: as for 5.2.1 except for D.

- **D** Headache persists for > 3 months after the injury to the head

5.2.1.2 Acute post-traumatic headache attributed to mild traumatic injury to the head

Diagnostic criteria:

- **A** Any headache fulfilling criteria C and D.
- **B** Injury to the head fulfilling both of the following:
  - **1** Associated with none of the following:
    - (a) Loss of consciousness for > 30 minutes
    - (b) GCS score < 13
    - (c) Post-traumatic amnesia lasting > 24 hours
    - (d) Altered level of awareness for > 24 hours
    - (e) Imaging evidence of traumatic head injury, such as intracranial haemorrhage and/or brain contusion
  - **2** Associated immediately following the head injury with one or more of the following symptoms and/or signs:
    - (a) Transient confusion, disorientation, or impaired consciousness
    - (b) Loss of memory for events immediately before or after the head injury.
    - (c) Two or more other symptoms suggestive of mild traumatic brain injury: nausea, vomiting, visual disturbances, dizziness, and/or vertigo, impaired memory and/or concentration
- **C** Headache is reported to have developed within 7 days after one of the following:
  - **1** The injury to the head
  - **2** Regaining consciousness following the injury to the head
  - **3** Discontinuation of medication(s) that impair ability to sense or report headache following the injury to the head.
- **D** Either of the following:
  - **1** Headache has resolved within 3 months after the injury to the head
  - **2** Headache has not yet resolved, but 3 months have not yet passed since the injury to the head.
- **E** Not better accounted for by another ICHD-3 diagnosis.

5.2.2 Persistent headache attributed to mild traumatic injury to the head

Diagnostic criteria: as for 5.2.1.2 except for D.

- **D** Headache persists for 3 months after the injury to the head.

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Table 35.1 Recent civilian and US active duty service member post-traumatic headache (PTH) studies.

Authors	Year/location	Number	Study design	Population	Key results
Blume et al. (23)	2012/US	462	Prospective cohort	Age 5–17 y; mTBI = 402; moderate–severe TBI = 60; controls = 122 (arm injury)	mTBI HA prevalence: after 3 mo = 43%; after 1 y = 41% Moderate–severe TBI prevalence: after 3 mo = 37%; after 1 y = 35% Control 3 mo = 26%; after 1 y = 34%
Dikmen et al. (10)	2010/US	732	Prospective case–control	Age > 16y; any TBI	TBI after 1 mo = 55%; after 1 y = 26% (if HA the week before)
Erickson (24)	2011/US	100	Retrospective cohort	Headache clinic; 100 consecutive soldiers with chronic PTH	77% had blast-related PTH; > 95% met migraine criteria
Faux and Sheedy (25)	2008/Australia	100	Prospective ED; case–control	Age > 16 y; moderate–severe TBI	Prevalence at time of evaluation = 100% At 1 mo = 30%; at 3 mo = 15%
Hoffman et al. (16)	2011/US	452	Prospective in-person enrolment; telephone interview at 3,6, and 12 mo	Moderate–severe TBI	Cumulative incidence 1 y = 71%; baseline prevalence = 47%; at 1 y = 44%
Hoge et al (26)	2008/US	2525	Cross-sectional survey	Soldiers after 1 y Iraq deployment	HA the only symptom associated with concussion adjusting for mood disorder
Kuczynski et al. (27)	2013/Canada	670	Prospective ED cohort Retrospective chart review of treatment cohort from brain injury clinic; telephone interview 7–10 d after injury and monthly until resolution	Age 0–18 y; mTBI	Prevalence of PTH at 16 days = 11%; at 3 mo = 8% ED cohort migraine = 54% Clinic cohort migraine = 39% (mixed HA, MOH, mood disorders with HA excluded)
Lieba-Samal et al. (28)	2011/Austria	100	Prospective telephone interview	Age 18–65 y (exclusions: whiplash; medication overuse, pre-existing chronic PTH)	Prevalence of acute PTH 7–10 d = 66% All resolved by 3 mo; migraine/probable migraine = 35%
Lucas et al. (29, 30)	2012/US 2014/US	452 212	Prospective in-person enrolment; 3, 6, and 12 mo telephone interview	Age > 16 y; 2012: moderate–severe TBI; 2014 mTBI	Moderate–severe TBI study: migraine/probable migraine = 52%; at 1 y = 54% mTBI study: cumulative incidence = 92% Migraine/probable migraine = 49%; 1 y = 49%
Stovner et al. (31)	2009/Lithuania	217	Prospective ED cohort; case–control; questionnaire at 3 mo and 1 y	Age 18–60; LOC < 15 min	Prevalence of HA at 3 mo = 65% Migraine at 3 mo = 19% and at 1 y = 21%
Theeler et al. (33,61)	2012/US 2012/US	1033	Cross-sectional, survey-based	Soldiers with concussion in post-deployment evaluation over 5 mo in 2008	HA in 98% of soldiers (PTH criteria in 37%). Migraine type = 89%; CDH = 20% (PTH criteria in 55%)

mTBI, mild traumatic brain injury; HA, headache; TBI, traumatic brain injury; ED, emergency department; MOH, medication overuse headache; LOC, loss of consciousness; CDH, chronic daily headache, mo, month; y, year.

Adapted from: Lucas, S. Post Traumatic Headache. In *Headache and Migraine Biology and Management*. Diamond S, ed. Elsevier, 2015; *Headache*, 53, 6, Theeler B, Lucas S, RIechers RG, Ruff RL, Posttraumatic headache in civilians and military personnel: a comparative clinical review, pp. 881–900, 2013.

were men injured in vehicle-related accidents, with an average age of 44 years. Seventy-one per cent reported headache during the first year. Prevalence was 46% at the initial inpatient interview and remained high, with 44% reporting headache 1 year after TBI. Headache consistency in this study (whether headache was reported at initial inpatient interview or at 3, 6, and 12 months after the injury) showed that although 34% of this head-injured population never had a headache following the injury, 23% had headache at every time point at which they were interviewed (16). In a follow-up study by the same group, using a similar headache assessment, a cohort of 212 individuals admitted to the hospital with mTBI and evaluated within 1 week after TBI, 91% reported new or worse headache (compared with before the injury) over the first year. The prevalence of new or worse headache was 54% within the first week of the injury and also remained high (58%) at 1 year after injury. In this cohort, 18% had headache at no time after injury and 41% had headache at all time-points after injury (30). Other studies have also reported a higher prevalence of PTH after mild versus more severe brain injury (3,20,21,34).

Post-traumatic headache risk factors

A prior history of headache was significantly related to PTH in several studies (16,27,28,30,31). Age appears to be inversely correlated

to PTH. Older age (> 60 years) had a lower prevalence of headache in a study of mTBI (30), as well as in a study of all severity levels of TBI (10). More controversial is whether females are more likely to have PTH than males. In the large, prospective studies discussed earlier, female sex was not a risk factor for new or worse PTH versus pre-injury in those following mild or moderate-to-severe brain injury (16,30). In a telephone interview of 168 patients 9–12 months after concussion or suspected concussion, a Danish study reported an adjusted odds ratio of 2.6 of women versus men for PTH (35). No sex difference was found between girls and boys with persistent PTH in a paediatric study after mild TBI either in an ED cohort or a clinic treatment cohort (27). Using a Veterans Administration 2011 database of over 470,000 Iraq and Afghanistan war veterans, headache diagnoses were found to be higher in women (18%) than in men (11%), with most of the difference due to higher prevalence of migraine. When adjusted for prior history of primary headache disorder, PTH was found to be less prevalent in women than in men (36).

Clinical characteristics of post-traumatic headache

Although PTH is one of the most prevalent secondary headaches classified in ICHD-3 (14), there are no defining clinical characteristics that would differentiate a PTH from another primary or secondary headache disorder (37). Following a TBI of any severity, a variety of headache symptoms may develop without specific location, severity, frequency, duration, or associated features, such as nausea, vomiting, photophobia, phonophobia, or presence of aura. In addition, the headache may change features from headache to headache or over time after injury. Most PTH has clinical characteristics that are similar to the primary headache disorders, although some are not classifiable according to ICHD-3 criteria. Whether phenotypic classification will be important as a diagnostic marker, guide successful treatment of PTH, or only be of epidemiological interest remains unknown. However, in an effort to describe PTH and to target treatment according to clinical characteristics, many studies have used the classification criteria for primary headache disorders to characterize PTH (18–33) (Table 35.1).

Recent studies using classification criteria support migraine or probable migraine as the most common type of PTH. An early review suggested that the headaches meeting tension-type headache (TTH) criteria were the most prevalent PTH; however, ICHD diagnostic criteria were not consistently utilized (19). In a large, longitudinal study of PTH following moderate-to-severe brain injury, migraine or probable migraine was the most common PTH phenotype. Migraine or probable migraine was found in > 52% of those reporting headache at initial evaluation, and in 54% of those with headache at 1 year. In those with no prior history of headache, migraine or probable migraine was found in 62% reporting headache initially and in 53% at 1 year (29).

Migraine or probable migraine was also the most common headache phenotype in a large study of headache after mTBI in civilians (30). These two headache types were found in 49% of patients, up to a year after injury, with TTH never > 40% of the total PTH types over that year. Importantly, these study populations are primarily males (> 71%) injured in vehicle accidents. The migraine or probable migraine headache type seen after TBI appears to be much more frequent in males than would be seen in primary migraine or probable migraine in the general population (38). Cervicogenic headache, a secondary headache with defining clinical features, made up 10% or fewer of classifiable headaches in these studies in which the major mechanism of injury was vehicle accidents (29,30).

Other studies of adult civilians in whom headache classification after mTBI was reported state that migraine (or probable migraine) followed by TTH (or probable TTH) were the most common headache types found (28,39). In a large cohort of children evaluated in an ED, migraine was found to be the most common headache type, reported in 55% of those children who had headache after mTBI (27). In studies reporting TTH as the most common PTH type after mTBI (31,40,41), some potential factors underlying differences in results might be selection of subjects, inpatient or outpatient specialty clinics, a long interval between injury to evaluation, and retrospective chart review. Some studies will report more than one headache type and others will take a hierarchical view of headache, only reporting migraine type, while others may present the PTH as mixed headache types.

PTH frequency is higher in those who have more severe PTH such as the migraine type. Civilians who had migraine or probable migraine PTH types were most likely to describe headaches occurring several days a week or daily when compared to those with TTH or cervicogenic headache type (29). Whereas in the general population, 4–5% of those with headache have chronic daily headache (CDH) (42,43), 23% of patients after moderate-to-severe TBI with migraine or probable migraine headache type reported a headache frequency of 15 days of headache per month or more over the year after TBI (29). After mTBI, of those who experienced headache several times a week or daily, 62% of the headache types were migraine or probable migraine (30). In another civilian population-based study, head and neck injury accounted for about 15% of CDH cases (44).

Although uncommon, some PTH phenotypes can present with clinical features of hemicrania continua (45), chronic paroxysmal hemicrania (46), short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) syndrome (47), and cluster headache (48). Although no significant relationship has been found between acute neuroimaging abnormalities and the presence or absence of PTH in a study of moderate-to-severe brain injury (49), secondary headache patterns associated with specific craniocerebral injuries are reported. For example, leakage of cerebrospinal fluid (CSF) can produce low CSF pressure headaches, or post-craniotomy headache can occur following surgical treatment of a TBI (50).

Sports-related post-traumatic headache

Approximately 20% of all civilian TBIs in the USA occurs in amateur athletic events through college level and is primarily mTBI (1,2,51). Approximately 90% of athletes are symptom-free within 1 month, but 10–20% may continue to have symptoms of PCS, including headache (52). Multiple episodes of TBI are more likely to have PTH that persists for longer than 1 month (53). One of the sports activities with the highest risk of concussion is American football (4,54). There have been several studies examining the relative playing position of athletes and intensity and frequency of contact, using both clinical evaluations, and visual and helmet-sensor information. Not surprisingly, offensive and defensive linemen, for example, may have frequent, short distance, lower-magnitude impacts, whereas running backs, wide receivers, linebackers, and even quarterbacks, may

experience fewer, but greater magnitude, head impacts due to high-speed tackling (55). In a study of 730 National Collegiate Athletic Association Division I football championship series athletes using a self-report questionnaire, there were no significant differences between diagnosed concussions and player position; however, there were significant differences in undiagnosed concussions based on reported post-concussive symptom frequency, the most being 'bell rung', dizziness, and headache. Offensive linemen returned to play or practice while experiencing symptoms more often than other position groups (56). Those who sustain more frequent, but lower intensity, head impacts, such as the linemen in this study, may see these symptoms as routine as they are experienced so often; the clinical relevance to brain function and long-term risk of neurodegeneration may not be appreciated until years in the future (57).

Post-traumatic headache in US soldiers and Veterans

Military combat-related TBI is complicated by extreme physical and psychological conditions of war (58). Many combat-related PTHs develop following blast exposure, although rarely is this an isolated causative mechanism and may include blast exposure followed by blunt trauma when hitting a vehicle or the ground (32,59,60). In one report, > 80% of 978 US Army soldiers reporting headaches after return from deployment were exposed to five or more blasts occurring within 60 feet (61). Similarly to the civilian population discussed earlier, PTH in this setting also may have a delayed onset beyond the 1-week latency requirements of the ICHD. In recently deployed soldiers, almost 40% of PTHs began within the first week after the mTBI, but 20% were reported within the first month and approximately 40% after the first month (32).

Also similar to studies in a civilian population, is the high prevalence of the migraine phenotype in PTH, as well as a high prevalence of chronic headache syndromes in the military. Recent studies in military and Veteran populations found occurrence of the migraine phenotype in 60–97% of cases, depending on the study population and methodology (18,32,62,63). Migraine was 5.4 times more likely in those who sustained a concussion than in those who did not (58). While migraine is also the predominant headache phenotype in this population, other headache types such as tension type, continuous headache, and cluster type did occur (18,64). CDH (> 15 days of headaches per month, > 4 hours per day) was common. Of 978 US Army soldiers with deployment-related concussion, 20% reported headaches on 15 or more days per month in the preceding 3 months, with a median of 27 headache days per month (65). Similarly, of 100 US Army soldiers with chronic PTH seen in a headache clinic, the average headache frequency was 17 days per month (62). Migraine features are present in 70% or more of the chronic PTH disorders in the military studies (58).

Post-traumatic headache mechanisms

Although there are animal models of PTH, the relevance of findings using these models to human headache mechanisms is difficult to determine.

As headache is the most common symptom after TBI, the initiation, as well as the persistence, of PTH may be linked to the physiological changes with TBI. The clinical similarities between the primary headache disorders and the PTH phenotypes may indicate shared physiological changes that develop after TBI and those seen in the primary headaches. Despite the mechanism of the initial injury and the magnitude of brain dysfunction, longer-term consequences of the initial injury, for example following subarachnoid haemorrhage, may initiate different and unique physiological changes, depending on the damage from initial injury.

Although the brain injury itself can cause extensive changes in all brain tissues, a reactive TBI response is also important and may have positive or negative long-term consequences. Changes associated with inflammation, including cytokine up- or downregulation, cerebral metabolic and haemodynamic alterations, axonal and glial injury, and neuropeptide and neurotransmitter activity abnormalities, have been reported after TBI.

Increased cytokine concentrations in the central nervous system (CNS), primarily driven by activated glia after injury are seen almost immediately. Post-mortem studies have shown elevated messenger RNA levels of interleukin 1, 6, and 10, and tumour necrosis factor- α (66). Elevated cytokine concentrations may have both pro- and anti-inflammatory functions in the postinjury response, and, in turn, affect permeability of the blood–brain barrier (BBB) (67) and the initiation of pain (68). Repetitive or prolonged microglial activation may be an important mechanism occurring with repetitive head trauma, as continual release of potentially pro-inflammatory cytotoxins could contribute to progressive symptoms (69,70). Direct BBB injury or a transient response to the injury exposes the brain to inflammatory and other components of peripheral blood into the CNS, which in itself can result in neuronal and glial changes that are indirect consequences of the injury. This can result in chemokine trafficking into the CNS, change in regulation of matrix metalloproteinases and Toll-like receptors among other mediators of inflammatory responses, which can affect neuronal-to-glial signalling, and even sensitization and maintenance of pain (71).

The mechanism that links TBI to postinjury headache is the subject of intense current research. Several likely important physiological processes may result from changes in meningeal, neuronal, glial, and vascular structural or functional changes that can lead to CSD (72) and trigeminovascular activation (73) following TBI.

Either CSD or trigeminovascular activation can increase calcitonin gene-related peptide levels, which may be involved in vasodilatation, neuroinflammation, and pain (74). Current research efforts are also focused on finding diagnostic markers for TBI, and common data elements have been defined by the Biospecimens and Biomarkers Working Group (75).

New imaging techniques, although not in clinical use, have contributed to findings in those with PTH after injury. Diffusion tensor imaging techniques showed decreases in fractional anisotropy in white matter tracts of patients developing chronic pain after TBI (76), and functional magnetic resonance imaging after TBI showed a disruption in the default mode network (77). No definitive relationships between structural or functional imaging as biomarkers after TBI and PTH have been found to date.

PTH management

The treatment of PTH is empirical, and for many practitioners, typing the headache according to primary headache clinical characteristics may serve as a guideline for management, but no definitive studies regarding medical management or the validation of this approach have been done. Often, TBI may be accompanied by other, severe injuries which may be addressed acutely with headache evaluated much later after injury. Those with PTH may seek care only if the headache becomes disabling, interfering with work or social function. There are many practitioners who may be involved with the care of a patient with PTH. If other injuries are still clinically important, a TBI clinic or rehabilitation clinic may be assessing PTH. Less often, a patient with PTH may seek a headache specialist or neurology clinic. Most PTH, however, is managed by a primary care practitioner or sports medicine specialist, if the injury is sports related.

Self-treatment of headache after TBI with over-the-counter (OTC) medication is the most likely treatment. In a study of 212 patients after mTBI, with a prevalence of headache not less than 58% of patients within 1 year after injury, > 75% of those with headache used acetaminophen or a non-steroidal anti-inflammatory drug (NSAID). Less than 5% of this group used a triptan, despite a migraine or probable migraine-type headache being the most common headache type (30,78).

In a review of PTH interventions, including pharmacological and non-pharmacological treatment, there were no class I studies and one class II study of a non-pharmacological intervention (79). Several class III studies have been published (80–83), and the Defense and Brain Injury Center has recommended PTH treatment for deployed and non-deployed soldiers based on class IV evidence (84).

To date, expert opinion suggests treatment of PTH according to its clinical characteristics using primary headache classification criteria (85,86). Based on similar clinical characteristics of PTH to primary migraine, probable migraine, and TTH, as well as other primary headache disorders, it is reasonable to provide acute headache care using a stratified approach. The goal of treatment of a PTH should be similar to the goal of treating a primary headache disorder: education regarding treating early with an effective acute therapy such as a triptan for a migraine-type headache, avoidance of medication overuse, and maintenance of a headache diary or other means of evaluation of PTH and effectiveness of treatment. Two treatment approaches are used for primary headaches such as migraine. Acute or abortive therapy treats a headache as it occurs and preventive therapy is used daily for high attack frequency, inability to use effective, acute therapy, or when response is suboptimal (87). Acute and preventive therapies are discussed in detail elsewhere in this book.

Medication overuse in a PTH population can be problematic and result in persistent headache. Potential adverse effects of overuse of any analgesic, such as gastritis or acute renal failure with prolonged high NSAID, is also of concern. This is likely because of high OTC use and self-treatment for headache (78), as well as treatment for other injuries such as musculoskeletal or joint injuries that can co-occur. Self-medication management may be a potential problem in those who have sustained a head injury. Assessment of cognitive limitations at the time of medication evaluation may necessitate the involvement of family members or caregivers when management with any therapy is discussed.

Conclusion

Headache is the most common physical symptom following TBI of any severity. It is highly prevalent in both adult and paediatric civilian, as well as military, populations. PTH has been classified in these populations using primary headache disorder classification criteria with the most frequent headache type meeting criteria for migraine or probable migraine. Currently, PTH management is empirical, with many providers using management strategies based on principles of stratified care and clinical similarity to primary headaches. This approach has not been validated, and whether or not similar phenotypes of primary headaches and PTH respond similarly to treatment is not known. Given the high incidence of TBI and prevalence of PTH, controlled, blinded clinical trials are needed to determine the most effective management of PTH.

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36

Cervicogenic headache

Nikolai Bogduk

Introduction

Other forms of secondary headache share the feature that the source of pain lies within the head (1). Cervicogenic headache has the distinction that, although the pain is perceived in the head, its source lies in the cervical spine. For these reasons, cervicogenic headache is less a form of headache and more a form of spinal referred pain. Consequently, the entity is more widely recognized by health professionals who treat spinal pain than it is by headache specialists or neurologists.

Historical background

The earliest reference to headaches and the neck can be traced back to 1860–1862 (2,3). The earliest, easily accessible publication is that of Holmes (4), who, in 1913, stated that headache could arise from the neck. Since that time, various theories as to its causes have been advanced but subsequently refuted (5–8).

No evidence has ever been provided for 'fibrositis' (4), 'rheumatic headache' (9–11), trigger points (12,13), or weakened fibro-osseous insertions (14,15) as a cause of headache. These conditions were diagnosed only on the basis of tenderness in the upper cervical muscles, but tender points in the neck occur in many forms of headache, including migraine (16–19), and are not indicative specifically of a cervical source of pain.

In 1926, Barré proposed that vascular headaches of the vertebral artery could be caused by irritation of the vertebral nerve by arthritis of the cervical spine (20), but studies in laboratory animals have shown that electrical stimulation of the vertebral nerve does not influence vertebral blood flow (21), and the vertebrobasilar system is remarkably resistant even to intra-arterial injections of vasoactive agents (21).

Some authors have attributed headaches to cervical spondylosis (22–28), but no study has shown that cervical spondylosis is significantly more common in patients with headache than in asymptomatic subjects.

Neuroanatomy

The neuroanatomical basis for cervicogenic headache is well understood (6–8). The structure of the trigeminocervical nucleus provides the anatomical substrate for referral of pain from the cervical spine to the head. The grey matter of the pars caudalis of the spinal nucleus of the trigeminal nerve is continuous with the apical grey column of the spinal cord (29–34). Nociceptive afferents of the trigeminal nerve descend in the spinal tract of the trigeminal nerve, and send collateral terminals not only into the pars caudalis of the spinal nucleus, but also into the dorsal horns of the upper three segments of the cervical spinal cord (30). Within these segments, nociceptive afferents of trigeminal origin converge onto second-order neurons that also receive afferents from the upper three cervical spinal nerves. Also, cervical afferents converge on neurons subtended by other cervical afferents. This convergence allows for upper cervical pain to be referred to regions of the head innervated either by cervical nerves (occiput and peri-auricular regions) or by the first division of the trigeminal nerve (parietal and frontal regions, and orbits).

This neuroanatomy dictates that the principal catchment area for possible sources of cervicogenic headache lies among those structures innervated by the upper three cervical nerves. These encompass intracranial sources and spinal sources. Of the intracranial sources, the inferior surface of the tentorium cerebelli, and the dura mater of the posterior cranial fossa are innervated by cervical nerves found in the meningeal branches of the hypoglossal and vagus nerves (35); the dura mater of the clivus is innervated by the upper cervical sinuvertebral nerves; and the vertebral artery is innervated by the vertebral nerve, which is formed by sympathetic efferents and cervical afferents (21,36). Of the spinal sources, the ventral rami of the first three cervical spinal nerves innervate the sternocleidomastoid muscle and trapezius (35); the C1 and C2 ventral rami innervate the atlanto-occipital and lateral atlanto-axial joints (37–39); the C1 dorsal ramus innervates the suboccipital muscles (35); the C2 and C3 dorsal rami innervate the larger posterior neck muscles and the C2–3 zygapophysial joint (40); and the C1–C3 sinuvertebral nerves innervate the C2–3 intervertebral disc

(41,42), and the transverse ligament and the alar ligament (43). The sensory innervation of the extracranial portions of the internal carotid artery has not been explicitly demonstrated, but is presumably also cervical in origin. To various extents, each of these structures has been incriminated as a source of cervicogenic headache.

Physiology

Frederick Kerr (44) provided the first physiological evidence of trigemino-cervical convergence. He mapped the sites in the C1–2 segment of the spinal cord that responded to electrical stimulation of both the trigeminal nerve and the sensory roots of the C1 or C2 spinal nerves.

Modern studies have demonstrated neurons in the lateral cervical nucleus of the cat that respond to electrical stimulation of both the superior sagittal sinus and the greater occipital nerve (45), and neurons in the C2 spinal cord segment of the rat that receive input from both trigeminal and cervical afferents (46,47). The latter included wide dynamic-range neurons and nociceptive-specific neurons, located in laminae V and V, and laminae I and II of the dorsal horn, which receive convergent input from Aδ and C fibres.

Electrical or chemical stimulation of trigeminal afferents sensitizes central neurons and increases their responses to cervical stimulation (46,47). Reciprocally, stimulation of cervical afferents sensitizes the responses of central neurons to trigeminal stimulation. Stimulation of C fibres in cervical afferents produce greater and more enduring increases in central sensitization than does stimulation of Aδ fibres (46), and cervical input from muscle produces a greater and longer-lasting increase in neural excitability than does cutaneous input (47).

Studies in humans

Studies in human volunteers have demonstrated the patterns of referred pain that can occur from cervical structures to the head. Electrical stimulation of the dorsal rootlets of C1 produces frontal headache (48). Noxious stimulation of the greater occipital nerve produces headache in the ipsilateral, frontal, and parietal regions (49). Noxious stimulation of the suboccipital muscles of the neck produces pain in the forehead (50–53). Distending the C2–3 intervertebral disc, but not lower discs, produces pain in the occipital region (54,55). Distending the C2–3 zygapophysial joint with injections of contrast medium produces pain in the occipital region (56), as does distending the lateral atlanto-axial joint or the atlanto-occipital joint (57). In normal volunteers, all segments from the occiput to C4–5 are capable of producing referred pain to the occiput. Referral to the forehead and orbital regions more commonly occurs from segments C1 and C2 (51).

Complementary studies in patients with headache have shown that some headaches can be relieved by anaesthetizing structures innervated by the C1, C2, or C3 nerves, such as the C2–3 zygapophysial joint (58–60), the lateral atlanto-axial joint (61–66), or the C3–4 zygapophysial joint (65,67). Of these, the C2–3 zygapophysial joint is the most common source, followed by the lateral atlanto-axial joint, and occasionally the joint at C3–4 (65–67).

Pain from particular structures or particular spinal segments does not consistently refer to specific sites, but certain tendencies have been observed (**Figure 36.1**) (65). Pain from C2–3 tends to be perceived across the lateral occipital region and into the forehead and orbital region. Pain from C1–2 also tends to gravitate to the orbital region, but otherwise more often occurs in the vertex or around the

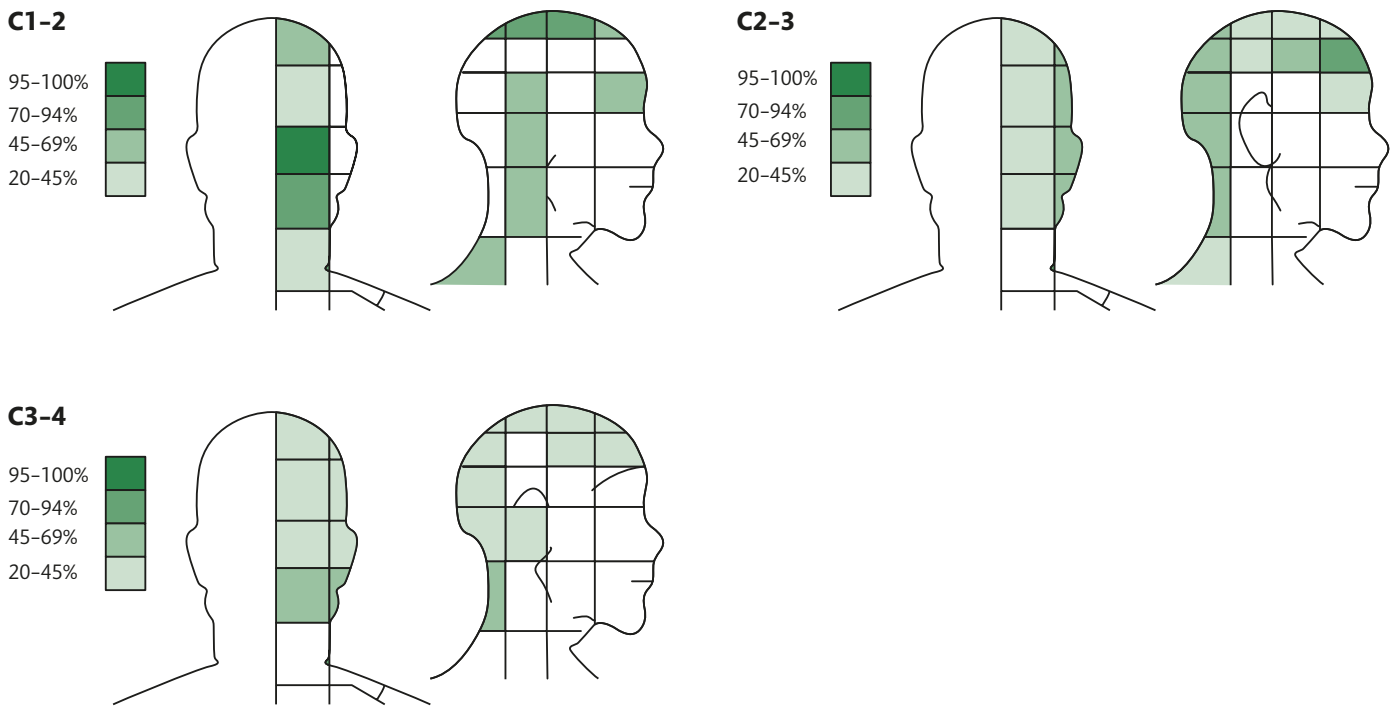

Figure 36.1 Maps of the distribution of pain in patients who were relieved of their headaches by controlled diagnostic blocks of the joints indicated. The shading reflects the proportion of patients who reported pain in the region indicated.

Adapted from *Pain Medicine*, 8, Cooper G, Bailey B, Bogduk N., Cervical zygapophysial joint pain maps, pp. 344–353. Copyright (2007) by permission of Oxford University Press.

ear. Pain from C3–4 tends to focus in the suboccipital region and upper cervical spine; when it does spread to the head, it is largely restricted to the posterior regions, sparing the forehead and orbit.

Contemporary conflicts

The cardinal issue concerning cervicogenic headache pertains to the mode of its diagnosis. Neurologists are accustomed to diagnosing headache on the basis of clinical features, perhaps coupled with medical imaging. Therefore, some neurologists sought to define and diagnose cervicogenic headache in this manner.

The clinical criteria, proposed in 1990 and revised in 1998 defined cervicogenic headache as a unilateral headache associated with evidence of cervical involvement, in the form of provocation of pain by movement of the neck or by pressing the neck, concurrent pain in the neck, shoulder, and arm, and reduced range of motion of the neck (68,69). Subsequent studies, however, showed that unilaterality was not unique to cervicogenic headache (70–72), nor was triggering of headache by neck movement or by pressure on the neck (73). Patients said to have cervicogenic headache have reduced pressure-pain thresholds (74) and impaired muscle function (75), but their scores in these features overlap considerably those of normal subjects, so that a valid diagnostic criterion cannot be supported. Similarly, radiographic abnormalities are either lacking in patients said to have cervicogenic headache (76,77), or have a distribution that overlaps that of normal subjects (78).

When tested for agreement between observers, the proposed clinical features of cervicogenic headache differ in their reliability. Whereas some were reliable, others lacked reliability (79,80). However, none has been shown to be a valid sign of a cervical source of pain.

Some authorities have developed a less dogmatic, clinical approach to diagnosis. Using a list of seven criteria, a diagnosis of cervicogenic headache could be offered qualified by two grades of certainty (**Box 36.1**) (81). A diagnosis of 'possible' cervicogenic headache could be offered if patients had 'unilateral headache' and 'pain starting in the neck'. Satisfying any three additional criteria promotes the diagnosis to 'probable' cervicogenic headache. The clinical features most strongly indicative of cervicogenic headache are 'pain radiating to the shoulder and arm', 'varying duration or fluctuating continuous pain', 'moderate, non-throbbing pain', and 'history of neck trauma'.

The definitive diagnosis of cervicogenic headache, however, requires demonstration of a cervical source of pain. Currently, the only means of doing so is by the application of controlled diagnostic blocks. Diagnostic blocks circumvent the difficulties of reliability and validity of clinical examination, and provide direct evidence of a cervical source of pain.

The revised criteria of the International Headache Society (IHS) reflect the tension between clinical diagnosis and diagnostic blocks

Box 36.1 The collapsed criteria for cervicogenic headache

1 Unilateral headache without side shift.
2 Symptoms and signs of neck involvement: pain triggered by neck movement or sustained awkward posture and/or external pressure of the posterior neck or occipital region, ipsilateral neck, shoulder, and arm pain, and reduced range of motion.
3 Pain episodes of varying duration or fluctuating continuous pain.
4 Moderate, non-excruciating pain, usually of a non-throbbing nature.
5 Pain starting in the neck, spreading to oculo-fronto-temporal areas.
6 Anaesthetic blockades abolish the pain transiently provided complete aanesthesia is obtained

Or sustained neck trauma a relatively short time prior to the onset:

7 Various attack-related phenomena: autonomic symptoms and signs, nausea, vomiting, ispilateral oedema and flushing in the periocular area, dizziness, photophobia, phonophobia, and blurred vision in the ipsilateral eye.

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Box 36.2 Diagnostic criteria for cervicogenic headache

Description

Headache caused by a disorder of the cervical spine and its component bony, disc and/or soft tissue elements, usually but not invariably accompanied by neck pain.

Diagnostic criteria

A Any headache fulfilling criterion C.
B Clinical and/or imaging evidence[1] of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache.[2]
C Evidence of causation demonstrated by at least two of the following:
  1 Headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion
  2 Headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion
  3 Cervical range of motion is reduced and headache is made significantly worse by provocative manoeuvres
  4 Headache is abolished following diagnostic blockade of a cervical structure or its nerve supply.
D Not better accounted for by another ICHD-3 diagnosis.[3,4,5]

Notes

1 Imaging findings in the upper cervical spine are common in patients without headache; they are suggestive but not firm evidence of causation.
2 Tumours, fractures, infections, and rheumatoid arthritis of the upper cervical spine have not been formally validated as causes of headache, but are accepted to fulfil criterion B in individual cases. Cervical spondylosis and osteochondritis may or may not be valid causes fulfilling criterion B, again depending on the individual case.
3 When cervical myofascial pain is the cause, the headache should probably be coded under '2. Tension-type headache'; however, awaiting further evidence, an alternative diagnosis of 'A11.2.5 Headache attributed to cervical myofascial pain' is in the Appendix.
4 Headache caused by upper cervical radiculopathy has been postulated and, considering the now well-understood convergence between upper cervical and trigeminal nociception, this is a logical cause of headache. Pending further evidence, this diagnosis is in the Appendix as 'A11.2.4 Headache attributed to upper cervical radiculopathy'.
5 Features that tend to distinguish 11.2.1 'Cervicogenic headache' from '1. Migraine' and '2. Tension-type headache' include side-locked pain, provocation of typical headache by digital pressure on neck muscles and by head movement, and posterior-to-anterior radiation of pain. However, while these may be features of '11.2.1 Cervicogenic headache', they are not unique to it and they do not necessarily define causal relationships. Migrainous features such as nausea, vomiting, and photo/phonophobia may be present with '11.2.1 Cervicogenic headache', although to a generally lesser degree than in '1. Migraine', and may differentiate some cases from '2. Tension-type headache'.

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for cervicogenic headache (Box 36.2) (82). They require evidence of a cervical source of pain, but the explanatory notes declare that clinical features that lack reliability or validity are not acceptable. In the absence of other evidence, controlled diagnostic blocks become the only means of establishing the diagnosis.

Refuted or contentious causes

Although various entities have been advanced as causes of cervicogenic headache, few have satisfied the IHS criteria. Congenital abnormalities are only incidental findings in some patients with headache, and have not been shown to cause pain. No evidence shows that the diagnosis of 'trigger points' as a cause of headache is either reliable or valid. Patients with rheumatoid arthritis can develop headache when their atlanto-axial joints become involved, but the diagnosis is evident from the systemic distribution of the disease. The evidence for osteoarthritis of the median atlanto-axial joint being a cause of headache is barely circumstantial (83,84).

A particular vexatious entity is occipital neuralgia. The IHS defines occipital neuralgia as 'paroxysmal jabbing pain in the distribution of the greater or lesser occipital nerves' (82). Paroxysmal lancinating pain is the hallmark of neuralgia and is the essential diagnostic criterion for occipital neuralgia. Explicitly, this definition does not apply to deep, aching pain in the occiput. This can arise from diseases of the posterior cranial fossa and base of skull (85) and the upper cervical joints (58–60). Indeed, the IHS comments that occipital neuralgia must be distinguished from occipital referral of pain from the atlanto-axial or upper zygapophysial joints (82).

Traditionally, it has been believed that occipital neuralgia is caused by irritation of the greater occipital nerve where it enters the scalp. However, there is no compelling evidence of such irritation. Lancinating occipital neuralgia has been recorded as a feature of temporal arteritis (86), in which case inflammation of occipital artery could affect the companion nerve. However, in the majority of cases of so-called occipital neuralgia no such pathology is evident. Also, anatomical studies have denied that occipital neuralgia is caused by entrapment of the greater occipital nerve where it pierces thetrapezius (40). The greater occipital nerve emerges from under an aponeurosis between the trapezius and the sternocleidomastoid. At surgery, this aponeurosis could be mistaken for 'scar' tissue.

Although Curwood Hunter and Frank Mayfield proposed that occipital neuralgia could be caused by compression of the occipital nerve between the posterior arch of the atlas and the lamina of C2 (87), and recommended treatment by greater occipital neurectomy, it has since been shown that the greater occipital nerve cannot be injured in this way (88,89). Indeed, in a later publication, Mayfield was more reserved about his earlier enthusiasm for greater occipital neurectomy and its success rate (90).

Entities with evidence

C2 neuralgia

The C2 spinal nerve runs behind the lateral atlanto-axial joint, resting on its capsule (38,39). Inflammatory or other disorders of the joint may result in the nerve becoming incorporated in the fibrotic changes of chronic inflammation (91,92). Release of the nerve relieves the symptoms. Otherwise, the C2 spinal nerve and its roots are surrounded by a sleeve of dura mater and a plexus of epiradicular veins, lesions of which can compromise the nerve. These include meningioma (93), neurinoma (94), anomalous vertebral arteries (95), and venous abnormalities, ranging from single to densely interwoven dilated veins surrounding the C2 spinal nerve and its roots (96) to U-shaped arterial loops or angiomas compressing the C2 dorsal root ganglion (91,95,96). Nerves affected by vascular abnormalities exhibit a variety of features indicative of neuropathy, such as myelin breakdown, chronic haemorrhage, axon degeneration and regeneration, and increased endoneurial and pericapsular connective tissue (95).

The pain associated with these pathological changes is intermittent, lancinating pain in the occipital region associated with lacrimation and ciliary injection. This pain satisfies the criteria for occipital neuralgia, but the pathology lies in the C2 spinal nerve, not in the greater occipital nerve. Consequently, the diagnostic criterion is complete relief of pain following local anaesthetic blockade of the C2 spinal nerve, or sometimes the C3 nerve (91). These blocks are performed under radiological control and employ discrete amounts (0.6–0.8 ml) of long-acting local anaesthetic to block the target nerve selectively (91).

In order to distinguish this condition from occipital neuralgia, as commonly understood—or misunderstood—it has been referred to as 'C2 neuralgia' (97). This term serves to draw attention away from the greater occipital nerve to the C2 spinal nerve, while still recognizing the occipital location of the pain.

Neck–tongue syndrome

Neck–tongue syndrome is characterized by acute, unilateral, occipital pain precipitated by sudden movement of the head, usually rotation, and accompanied by a sensation of numbness in the ipsilateral half of the tongue (98) (see also Chapter 28). The pain appears to be caused by temporary subluxation of a lateral atlanto-axial joint, whereas the numbness of the tongue arises because of impingement, or stretching, of the C2 ventral ramus against the edge of the subluxated articular process (39). The numbness occurs because proprioceptive afferents from the tongue pass from the ansa hypoglossi into the C2 ventral ramus (98). Neck–tongue syndrome can occur in patients with rheumatoid arthritis or with congenital joint laxity (99). Hypomobility in the contralateral lateral atlanto-axial joint may predispose to the condition (100).

Lateral atlanto-axial joint pain

Diagnostic blocks of the lateral atlanto-axial joint require injection of a small volume of local anaesthetic into the joint, under fluoroscopic guidance (Figure 36.2) (101). Certain patients can be relieved of their headache by such blocks (61–66). One study attributed the pain to radiographically evident osteoarthritis (61), but such arthritis is not always evident. In post-traumatic cases, the responsible lesions might include capsular rupture, intra-articular haemorrhage, and bruising of intra-articular meniscoids, or small fractures through the superior articular process of the axis (102). In one study, the source of pain could be traced to the lateral atlanto-axial joints in 16% of patients presenting with headache (64), while in another study the prevalence was 13% (103).

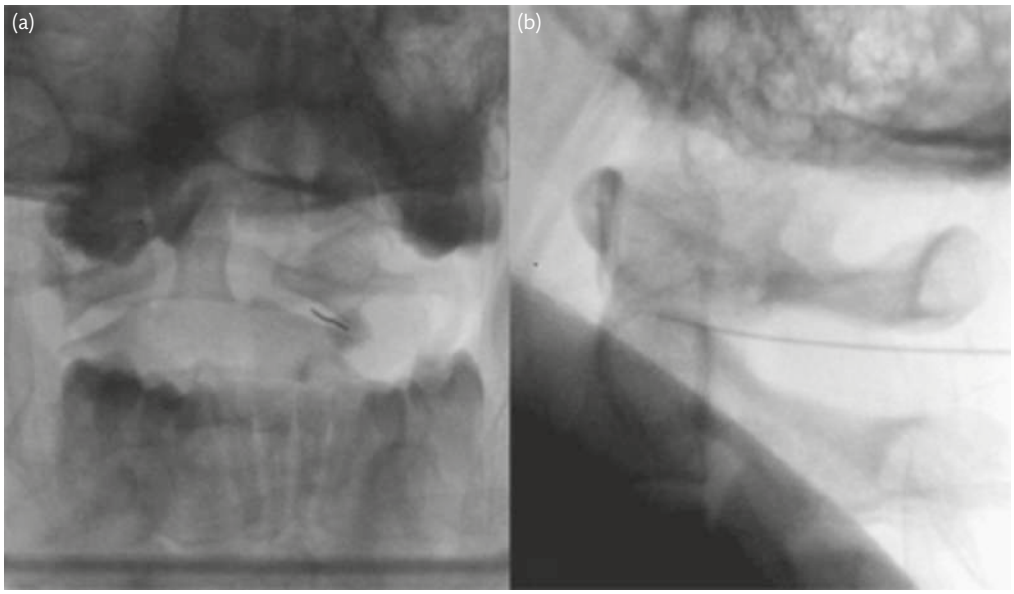

Figure 36.2 Fluoroscopy images of a needle in place for an intra-articular block of the right lateral atlanto-axial joint. (A) Antero-posterior view. (B) Lateral view.

Discogenic pain

There is some evidence to implicate the C2–3 intervertebral disc as a source of cervicogenic headache. Stimulation of this disc reproduces the pain suffered by some patients with headache (54,55). Arthrodesis of that disc has been reported to relieve headache (104). The nature of the causative pathology remains unknown.

Third occipital headache

The C2–3 zygapophysial joint is innervated by the third occipital nerve (40). The joint can be anaesthetized by blocking the third occipital nerve under fluoroscopic guidance (Figure 36.3) (105). Headache stemming from the C2–3 zygapophysial joint, therefore, can be relieved by third occipital nerve blocks, and, accordingly, has been named third occipital headache.

In the past, the pathology that causes pain from cervical zygapophysial joints was elusive. Experimental studies in laboratory animals have now shown that these joints can become a source of persistent nociception when their capsules are subjected to submaximal strain injuries (106,107). This provides the pathophysiological basis for neck pain and headache after injury to these joints, and complements the clinical studies concerning the prevalence of cervical zygapophysial joint pain (107).

A study using controlled diagnostic blocks established that, in patients with neck pain after whiplash, the prevalence of third occipital headache was 27% (60). Among patients in whom headache was the dominant complaint, the prevalence was 53% (95% confidence interval 37–68%).

A significant feature of patients in whom third occipital nerve blocks have been positive is that all had a history of trauma. This reinforces 'history of trauma' as a cardinal clinical feature for 'probable' cervicogenic (Table 36.1). No studies have shown that third occipital headache occurs without a history of trauma.

Figure 36.3 Lateral fluoroscopy view of a needle in place for a right third occipital nerve block.

Differential diagnosis

Two groups of conditions constitute the important differential diagnosis of cervicogenic headache. Each is distinguished from cervicogenic headache by features other than pain. They are disorders of the posterior cranial fossa, and aneurysms of the vertebral or internal carotid arteries.

As they are innervated by cervical nerves, disorders of the posterior cranial fossa can have a distribution of referred pain similar to that of cervicogenic headache. These disorders include tumours, which distend the dura mater of the posterior cranial fossa, and haemorrhage or meningitis, which irritate the dura chemically. These conditions are distinguished from cervicogenic headache by their mode of onset and by their associated features, such as neurological signs, systemic illness, and meningismus.

Less distinctive, at onset, is headache due to aneurysm of either the vertebral artery or the internal carotid artery. Headache is the

most common presenting feature of internal carotid artery dissection (108,109), and may occur together with neck pain (109). Headache is also the cardinal presenting feature of vertebral artery dissection. In both instances, some 60–70% of patients present with headache, typically in the occipital region, although not exclusively so (109–111). However, following the onset of headache, cerebrovascular symptoms and signs rapidly evolve, and declare the nature of the condition.

A case has been reported of cervicogenic headache caused by a lymph node metastasis infiltrating the cervical plexus (112). This case illustrates that cervical causes of headache need not be restricted to musculoskeletal structures.

Investigations

Imaging

There is no evidence that medical imaging is diagnostic of any cause of cervicogenic headache. Imaging is indicated only in patients who exhibit neurological signs. In that context, however, imaging is used is to determine the cause of the neurological abnormality, not necessarily the cause of pain.

In patients with cardiovascular risk factors or a history of neck distortion or cervical manipulation, aneurysm needs to be considered. For this entity, magnetic resonance angiography is the appropriate investigation.

Manual examination

Manual therapists contend that they can diagnose symptomatic joints by examining the cervical spine. Previously, this belief was based on one small study (113), but that study has now been refuted by a larger study, using more rigorous diagnostic criteria and more rigorous statistical analysis (114). Manual examination, therefore, lacks a foundation as a diagnostic test for cervicogenic headache.

Diagnostic blocks

Diagnostic blocks are the mainstay of diagnosis for cervicogenic headache (7,8,105). Only by these means can a cervical source of pain be established in a valid manner. However, in order for blocks to be valid, they must be conducted under controlled conditions (115–117).

In many studies that have used diagnostic blocks in the investigation of cervicogenic headache, controls were not implemented (5,115). Therefore, the results are uninterpretable. Of particular concern, is the common use of blocks of the greater occipital nerve. This nerve supplies no structure that is known to be a source of chronic pain. It supplies only the skin of the scalp and the occipitalis muscle. Consequently, a response to a greater occipital nerve block is not evidence of a cervical source of pain. Nor can blocks be considered to be target-specific for the nerve when they involve volumes such as 5 ml (74) or 10 ml (118,119) of local anaesthetic (115).

Given that stimulation of the greater occipital nerve facilitates responses in the trigeminocervical nucleus to noxious stimulation of the dura mater (46), it may be that greater occipital nerve blocks downregulate non-specific headache mechanisms or dysnociception, and do not imply a cervical source of pain. Circumstantial evidence favours this contention. Greater occipital nerve blocks relieve pain, temporarily, in substantial proportions of patients with migraine, cluster headache, and hemicrania continua (120). A positive, greater occipital nerve block, therefore, cannot be a specific test for cervicogenic headache.

To date, in the diagnosis of cervicogenic headache, third occipital nerve blocks are the only blocks that have been subjected to controls. Consequently, C2–3 zygapophysial joint pain is the only cause of cervicogenic headache for which there are valid diagnostic data. Third occipital nerve blocks are performed under fluoroscopic guidance, using aliquots of 0.3 ml of local anaesthetic (**Figure 36.3**) (105). They are controlled by using local anaesthetic agents with different durations of action, on two separate occasions (60,115–117).

Lateral atlanto-axial joint blocks are a complement to third occipital nerve blocks. They involve injecting local anaesthetic into the cavity of the joint (**Figure 36.2**), and serve either to pinpoint or to exclude a source of pain in that joint (101). They can be performed in a controlled fashion by first establishing that blocks of the C2–3 joint do not relieve pain, or by testing the joint with intra-articular injections of normal saline.

For patients with lancinating, occipital pain, C2 spinal nerve blocks are required to confirm the diagnosis of C2 neuralgia. The nerve can readily be blocked, under fluoroscopic guidance where it lies behind the lateral atlanto-axial joint (38).

Treatment

A variety of treatments have been used and advocated for cervicogenic headache (121,122). They can be grouped according to whether a specific source of pain is targeted or not, and whether the source has been presumed or diagnosed using a valid procedure. Intriguingly, success—in terms of degree of relief and duration of relief—is conspicuously greater when treatments target a diagnosed source of pain.

No source

Into this category fall conservative therapies, few of which have been vindicated by evidence. No drug has been claimed to be effective for cervicogenic headache, let alone shown to be so. Transcutaneous electrical nerve stimulation is partially effective in some patients, but only for a short time (123). Onabotulinum toxin is no more effective than placebo (124). Manual therapy is commonly used, but most of the literature consists of case reports or case series (3). The few randomized controlled studies provided follow-up of only 1 or 3 weeks, and provided conflicting results (3).

The largest and most recent study of conservative therapy showed that treatment with manual therapy, specific exercises, or manual therapy plus exercises was significantly more effective at reducing headache frequency and intensity than was no specific care by a general practitioner (125). Manual therapy alone, however, was not more effective than exercises alone, and combining the two interventions did not achieve better outcomes. Some 76% of patients achieved a > 50% reduction in headache frequency at the 7-week follow-up, and 35% achieved complete relief. At 12 months, 72% had > 50% reduction in headache frequency, but the proportion that had complete relief was not reported. Corresponding figures for reduction in pain intensity were not reported.

Presumed source

For most treatments in this category the greater occipital nerve has been targeted, for a presumed diagnosis of greater occipital neuralgia. Injection of depot methylprednisolone onto the greater occipital nerve can produce temporary relief (126), but no studies have explored the benefit of repeat injections in providing lasting relief. Surgical 'liberation' of the nerve (127), or excision of the greater occipital nerve, also provide temporary relief in some 70–80% of patients (128), but pain typically recurs, and the procedure cannot be repeated to reinstate relief.

Pulsed radiofrequency applied to the greater occipital nerve is no more effective than injection of methylprednisolone and bupivacaine onto the nerve, with about 50% of patients reporting 50% relief of pain at 9 months (129). Pulsed radiofrequency has also been applied to the C2 ganglion but described only in case reports (130,131).

A novel intervention has been the injection of processed, autologous, adipose tissue onto the greater occipital nerve. Nineteen of 24 patients were said to have had a good clinical response (not otherwise defined) at 3 months (132).

In other studies the lateral atlanto-axial joint has been targeted, but without evidence that prior diagnostic blocks had relieved the headache. In one study, 32 patients were treated with an intra-articular injection of a 1-ml mixture of triamcinolone and bupivacaine; and 25% reported at least 50% relief at 3 months (103). In another study, 86 patients were treated with intra-articular pulsed radiofrequency, and 43 reported 50% relief at 6 months, with 38 continuing to have relief at 12 months (133).

Diagnosed source

In one study, patients were selected for surgery if they satisfied the clinical criteria for 'cervicogenic headache' and obtained relief of headache from diagnostic blockade of the C2 spinal nerve (134). They underwent decompression and microsurgical neurolysis of the C2 spinal nerve, with excision of scar, and ligamentous and vascular elements that compressed the nerve. Fourteen of 31 patients were rendered pain-free. Details on the remaining patients are incomplete, but, ostensibly, 51% gained what was called 'adequate' relief, and 11% suffered a recurrence.

For patients whose headache can be relieved by lateral atlanto-axial joint blocks, an option for treatment is arthrodesis of the joint. The surgical literature attests to complete relief of pain being achieved, albeit in small numbers of patients, for over 2 years (135–137).

In those patients in whom the source of headache can be traced to the C2–3 intervertebral disc, disc excision and anterior cervical fusion reportedly can be effective (104). For pain from the C2–3 zygapophysial joint, intra-articular injection of steroids might provide relief for a small proportion of patients (138).

A minimally invasive treatment for a diagnosed and targeted source of pain is thermal radiofrequency neurotomy. In this treatment, an electrode is introduced percutaneously in order to coagulate the nerve or nerves shown to be responsible for mediating the headache, on the basis of controlled diagnostic blocks of those nerves (Figure 36.4). The available evidence shows that the effectiveness of radiofrequency neurotomy is contingent on the rigour of diagnosis and the rigour of treatment.

Three controlled trials have provided salutary evidence on practices that are not effective (139–141). Radiofrequency neurotomy is not effective: when patients are selected for treatment simply on the basis of clinical criteria; when nerves are indiscriminately targeted, without having been subjected previously to controlled diagnostic blocks; or when techniques for radiofrequency neurotomy are used that have not been validated (8,142,143).

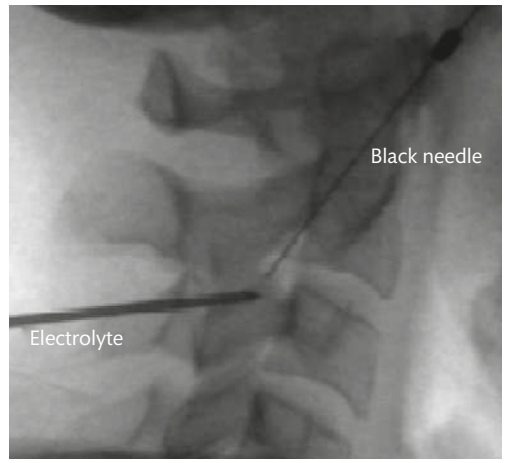

Figure 36.4 Lateral fluoroscopy view of an electrode in place for third occipital thermal radiofrequency neurotomy.

A block needle lies nearby for administration of local anesthetic if required.

Radiofrequency neurotomy becomes effective when patients are selected whose headache has been completely relieved by controlled diagnostic blocks of the target nerve (or nerves), and when meticulous surgical technique is used. For headaches stemming from the C2–3 zygapophysial joint, the diagnostic requirement is complete relief of pain from controlled third occipital nerve blocks (105), and standards for the execution of third occipital neurotomy have been defined (143). For headaches stemming from the C3–4 zygapophysial joint the diagnostic requirement is complete relief of headache from controlled C3, C4 medial branch blocks (144), and the treatment requires C3, C4 medial branch neurotomy (143).

If these diagnostic criteria are satisfied, and the correct technique is used, complete relief of pain can be achieved in 88% of patients, for a median duration of some 297 days (145). Such results have been corroborated by second (146) and third (147) independent studies.

Similar outcomes have been reported in patients whose headache could be relieved by controlled blocks of the C3, C4 medial branches (148). After thermal radiofrequency neurotomy of these nerves, > 70% of patients maintained at least 75% relief of their headache at 6 and 12 months.

For patients in whom headaches recurs, relief can be reinstated by repeating the neurotomy. By repeating neurotomy as required, some patients have been able to maintain relief of their headache for > 2 years (145), for up to 5 years (147), and beyond (149).

A study that has escaped attention in the literature explored the effectiveness of arthrodesis in the treatment of proven cervicogenic headache (150). Patients presenting with chronic headache were investigated using diagnostic blocks of the C2 and C3 nerve roots, and diagnostic blocks of the C2–3 and C3–4 zygapophysial joints conducted on separate occasions. Based on complete, or near complete, relief of headache following nerve root blocks and likewise

following zygapophysial joint blocks, 34 patients underwent posterior fusion of C1–2–3 using Brook's triple-wire fusion. Another 10 patients underwent fusion variously at C1–2, C2–3, or C1–2–3 based on positive responses to nerve root blocks but no response to zygapophysial joint blocks.

Before treatment, all 44 patients had severe or excruciating headache, rated as 8/10, 9/10, or 10/10 on a visual analogue scale. No evidence of injuries to the upper cervical joints was evident on pre-operative imaging, using flexion–extension radiographs, computed tomography, and magnetic resonance imaging (MRI). During surgery, the capsule of the C2–3 zygapophysial joint was judged to be disrupted in 36 patients. Deeper joints, such as the lateral atlanto-axial joints could not be inspected.

At 1 year after surgery, three patients had no pain, 22 had only mild pain, and 16 had moderate pain, in all cases rated as less than 5/10. These outcomes were sustained at 4 years, when seven patients had no pain, 22 had mild pain, and 10 had moderate pain. During this period of follow-up, in only two patients did pain scores deteriorate to pre-operative levels.

This study provides corroborating evidence that in patients with severe headaches, injuries to the upper cervical joints can escape detection using conventional imaging, but can be detected using diagnostic blocks and verified at surgery. Furthermore, the outcomes achieved invite consideration of posterior cervical fusion as an option for the treatment of severe, otherwise intractable, cervicogenic headache.

Clinical pathway

A clinical pathway has been recommended for the efficient management of cervicogenic headache (142). The pathway involves a disciplined approach to diagnosis, and uses treatments for which there is reasonable evidence of effectiveness but abjures those treatments for which evidence of lasting and worthwhile effect is lacking.

The primary indicator that a patient might have cervicogenic headache is pain in the occipital region or pain starting in the neck. However, even so, other forms of headache need to be considered, and excluded, before proceeding. If other conditions have been excluded, a diagnosis of 'possible' cervicogenic headache can be made.

The differential diagnosis includes posterior fossa lesions and aneurysms of either the vertebral artery or internal carotid artery. If these are possible or suspected, investigations with MRI or magnetic resonance angiography are indicated. In that event, cervicogenic headache is no longer a consideration, and the patient exits the clinical pathway.

If the patient has lancinating pain a diagnosis of occipital neuralgia can be pursued. This will entail performing C2 spinal nerve blocks, in order to confirm the diagnosis.

A diagnosis of 'probable' cervicogenic headache can be formulated if the patient has dull, aching pain that is continuous or fluctuating in intensity, associated with pain radiation into the shoulder, or a history of trauma. Such a level of certainty in the diagnosis can be adequate if conservative therapy is pursued.

The only conservative therapy for which there is any strong evidence of efficacy is manual therapy coupled with exercises. Most patients in primary care should benefit from this intervention.

Patients who do not benefit can be investigated more intensively. Since the pretest probability is highest for C2–3 zygapophysial joint pain, investigations should start with third occipital nerve blocks. If controlled blocks are positive, the patient can be treated with third occipital radiofrequency neurotomy. Intra-articular injection of steroids is a plausible, less destructive option, but lacks a definitive evidence base. If radiofrequency neurotomy is not available, posterior arthrodesis of C2–3 can be entertained.

If C2–3 blocks are negative, the next step is to test for lateral atlanto-axial joint pain with C1–2 blocks. If these are positive, treatment by arthrodesis can be considered.

If C1–2 blocks are negative, the C3–4 zygapophysial joint should be tested. If blocks are positive, treatment is possible with C3,4 medial branch radiofrequency neurotomy.

If C3–4 blocks are negative, the only remaining option is to test for C2–3 disc pain by discography. If discography is positive, treatment by arthrodesis can be considered.

In patients with sources of pain at multiple levels, such as C2–3 and C1–2, posterior fusion of both segments can be considered.

If discography and blocks of the joints of the upper three cervical segments all prove negative, there are no further, established investigations to pursue. The patient and their management should be revaluated. Either the diagnosis is not cervicogenic headache, or the patient has a cervical cause of pain that cannot be pinpointed using currently available technology.

The options may be to treat the patient palliatively, by providing non-specific pain-relief, or to enrol them in whatever ethics-approved study is available of procedures that have experimental or investigational status. Such procedures might include, but are not limited to, atlanto-occipital joint blocks, pulsed radiofrequency, implanted greater occipital nerve stimulation, or procedures directed at suboccipital muscles as the sources of pain. Ethics-approved studies guarantee patient safety, and protect them from unwittingly being subjects to practitioners who are no more than experimenting with untested and unproven procedures, without disclosing to the patient that they are doing so.

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37

Headache and neurovascular disorders

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Headache as a risk factor for neurovascular disorders

The relationship between migraine, ischaemic stroke, and elevated cardiovascular Framingham risk factors has been a well-documented association in case–control, cohort, observational studies, and population-based studies. Individuals with migraine have a twofold increased risk of ischaemic stroke (1–3). The risk of stroke appears to be independent of typical vascular risk factors and is best established in those with migraine with aura (MA), especially in women younger than 45 years of age (4,5). Smoking and the use of oral contraceptive agents appear to magnify the risk substantially (6,7). The risk also appears to increase with increasing migraine attack frequency (4). The risk of stroke in women with migraine has also been demonstrated in those older than 45 years of age. In the Women's Health Study, MA was associated with incident ischaemic stroke (hazard ratio (HR) 1.70, 95% confidence interval (CI) 1.1–2.6) and most evident for those < 55 years of age at baseline (HR 2.25, 95% CI 1.3–3.9) (6). MA was also found to be a risk factor for myocardial infarction (MI), coronary revascularization, and death due to cardiovascular disease. Similar results suggest that the risk of adverse cardiovascular events in patients with migraine may also be seen in men over the age of 45 years (8).

Several population-based studies have also linked migraine and asymptomatic brain infarctions. In a prospective longitudinal population based study (Cerebral Abnormalities in Migraine, an Epidemiological Risk Analysis (CAMERA)) in the Netherlands, migraine was associated with an increased likelihood of asymptomatic cerebellar infarct-like lesions (see also Chapter 10) (9,10). Although the risk was similar in women with and without aura, the risk was highest in those with MA and a frequency of more than one attack per month (odds ratio (OR) 15.8, 95% CI 1.8–140). These findings were independent of traditional cardiovascular risk factors (11). The association between MA and late-life infarct-like lesions in the cerebellum was also demonstrated (OR 1.4, 95% CI 1.1–1.8) in a population-based prospective study in Iceland. This study evaluated older adults (mean age 51 years) with migraine and also demonstrated that the risk of these asymptomatic infarcts was stronger in women (OR 1.9, 95% CI 1.4–2.6) (12). Finally, the presence of infarct-like lesions was confirmed (OR 12.4, 95% CI 1.6–99.4; p for trend = 0.005) by another population-based study, but the lesions were not confined to the cerebellum or the brain tissue supplied by the posterior cerebral circulation (13).

Migraine has also been shown to be a risk factor for adverse cerebrovascular and cardiovascular outcomes during pregnancy. In a recent systematic review, an increased risk of gestational hypertension (OR 1.23–1.68), pre-eclampsia (OR 1.08–3.5) and ischaemic stroke during pregnancy (OR 7.9–30.7) was demonstrated in those with migraine compared to those without. An association between migraine and increased risk of acute MI and heart disease (OR 4.9, 95% CI 1.7–14.2), and thromboembolic events during pregnancy (deep venous thrombosis OR 2.4, 95% CI 1.3–4.2; pulmonary embolus OR 3.1, 95% CI 1.7–5.6) was also demonstrated (14).

Headache as symptom of neurovascular disorders

Headache is a frequently encountered symptom in neurovascular disorders. It can occur at different stages such as at stroke onset, during the first days after stroke or as delayed headache in the chronic phase. Although headache is more frequent in certain subtypes of neurovascular diseases, it is often not useful in clinical practice to discriminate between different stroke subtypes. The start of the headache, however, can sometimes point towards a particular diagnosis, especially in case of a thunderclap onset (see Chapter 34). In certain vascular diseases, such as subarachnoid haemorrhage (SAH), reversible cerebral vasoconstriction syndrome (RCVS), cervical artery dissection (CAD), and cerebral venous sinus thrombosis (CVST), headache can be the only presenting symptom, which makes the diagnosis of these often serious diseases challenging. The frequency and nature of headache symptoms differ between different neurovascular diseases (**Table 37.1**).

Ischaemic stroke and transient ischaemic attack

An ischaemic stroke occurs as a result of an obstruction within a blood vessel supplying blood to the brain. This obstruction can be persistent, causing permanent damage, or it can be transient, without leaving any clinical or radiological deficit (transient ischaemic attack (TIA)). Most physicians associate headache primarily with a haemorrhagic cause of stroke, but this is incorrect as headache is also a frequently reported symptom in patients with cerebral ischaemia.

Table 37.1 Overview headache characteristics per subtype of neurovascular disease.

Neurovascular disease	Headache frequency (%)	Headache nature*	Associated factors†
Ischaemic stroke and TIA	14–38	Pressure like, throbbing	Young age, female sex, history of migraine
Intracerebral haemorrhage	34–57	Tension type, migraine type	Cerebellar or lobar location, transtentorial herniation
Subarachnoid haemorrhage	99	Thunderclap headache	Sentinel headache, preceding 1–3 days
Cerebral venous sinus thrombosis	70–90	Band-like, throbbing, thunderclap headache	Focal neurological deficits, seizures, papilloedema
Reversible cerebral vasoconstrictor syndrome	94	Thunderclap headache, recurrent attacks	Anxiety and depression are aggravated by chronic headache
Cervical artery dissection	50	Throbbing, constrictive	Neck pain, history of migraine
Arteriovenous malformation	25–56	Migraine (especially migraine with aura)	History of migraine (with aura), larger nidus volume, tortuosity of the feeding artery
Unruptured aneurysm	Unknown	Unknown	Headache symptoms may decrease or increase after endovascular treatment
Cavernoma	31–65	Tension type, migraine type	History of migraine
Cerebral angiitis	57–90	Divers	Jaw claudication in case of giant cell angiitis

TIA, transient ischaemic attack. *Headache nature that is most frequently described in patients. †Predictors of headache prevalence or concomitant factors.

The prevalence of headache at presentation of ischaemic stroke varies between 7% and 38% (15–22). The differences in prevalence are possibly explained by study design and method of headache retrieval. Recent prospective series report frequencies varying from 14% to 38% (20–22). Rarely, headache is the most prominent or even sole symptom of ischaemic stroke (23,24).

Headache associated with ischaemic stroke is related to certain clinical and stroke characteristics. It appears to occur more often in women and patients with a history of migraine (15,16,18,19,22). In contrast, patients with a history of hypertension and older patients seem to have a lower headache prevalence (18,19,21,22,25). In patients with lacunar infarctions, leukoaraiosis was less frequent and less severe in patients without headache (26). Headache has been associated with relatively low (< 120 mmHg systolic and < 70 mmHg diastolic) or very high blood pressure (systolic blood pressure >200 mmHg) on admission (18,27). Other less frequently reported and therefore more controversial risk factors are not smoking and use of warfarin (25,28).

Headache at symptom onset is relatively more common in infarctions located in the posterior circulation than in the anterior circulation (22,25,29). One study found a relation with cerebellar stroke and not with other brainstem locations (18). Although headache is often associated with cortical located lesions, several studies reported headache in lacunar infarctions, with a prevalence ranging from 10% to 23% (20,25,30). The size of the lesions was found to increase headache prevalence, but not headache severity, in two studies (21,28). The large scale of the Stroke in Young Fabry Patients (SIFAP1) study, which included 4431 young stroke patients, enabled multivariable analyses and revealed lower age, female sex, size of the largest lesion, and localization in the vertebrobasilar territory as independent predictors for headache during the ischaemic event (21). Until now, no clear association between headache and stroke aetiology has been demonstrated, although some studies found headache to be more common with cardioembolic stroke and large artery atherosclerosis and less common with small-vessel disease (15,18,25). Interestingly, another study found that headache was more common in patients without atherosclerosis in the anterior circulation (22).

Concomitant headache most often starts at onset or within the first one day after onset of ischaemic stroke and lasts, according to a study including both patients with ischaemic stroke and intracerebral haemorrhage (ICH), on average 4 days (31). Headache associated with ischaemia is found to be bilateral in 55% of cases. When unilateral, the headache appears to be more often ipsi-lesional than contralesional (16,31). This suggests that the presence of headache may be associated with pathophysiological mechanisms in and around the ischaemic area and not just a general sign of stress, raised blood pressure, or intracranial hypertension. If the headache has an acute onset and is located in the neck, behind the eye or the ear, a CAD as the cause of the infarction should be considered (see 'Cervical artery dissection'). In ischaemic stroke, headache symptoms are generally reported to be mild to moderate, but in cases of ischaemia in locations around the putamen or thalamus and in the posterior circulation severe pain has been described (17,21,28). Concomitant headache often has no specific features and is usually described as continuous, pressure-like, throbbing or non-throbbing (32).

In the long term, ischaemic stroke patients can develop chronic headache. After 6 months, 13% of patients reported newly developed headache in a prospective study of 299 patients (33). In a population-based study, 10% of 608 post-stroke patients reported headache 2 years after the event (34). In contrast, some patients with a history of migraine report improvement of their migraine symptoms after stroke (35–38).

Headache can also be one of the presenting symptoms of a TIA with a prevalence similar to cerebral infarction in some studies. In the SIPFAP1 study, headache was as frequent in TIAs (30%) as in ischaemic stroke (21). Because TIA symptoms can mimic a migraine aura, differentiation from a migraine attack can sometimes be challenging, especially in younger patients with visual or sensory symptoms. Generally, the progression of symptoms over time is considered to be the most important distinctive feature of migraine aura versus the sudden symptom onset in patients with true TIAs.

Migrainous infarction

Rarely, an ischaemic stroke starts as migraine aura that subsequently transfers into a cerebral infarction (see also Chapter 10). If a migraine aura persists longer than 60 minutes a migrainous infarct should be suspected and immediate imaging is indicated. Around 0.2% of ischaemic stroke cases seem to be caused by a migrainous infarction (39). In younger patients, migrainous infarction is reported to be more prevalent than in adults (40). In addition, migrainous infarction is 2–3 times more prevalent in women, which may very well be explained by the fact that MA is around three times more prevalent in women as well (41,42). The incidence of migrainous infarction may be overestimated, as other possible disorders leading to stroke should be ruled out so the diagnosis is dependent on the extent of radiological and cardiac work-up. Also, in younger patients, where migrainous infarction incidence is highest, the prevalence of MA and cryptogenic stroke are also relatively high (43).

Migrainous stroke is predominantly located in the posterior circulation (70–82%) (39,44). In a study of 18 patients in whom magnetic resonance imaging (MRI) was performed, 71% had lesions in the posterior circulation and 29% in the territory of the middle cerebral artery. Small lesions were present in 65% and multiple lesions were found in 41% of patients (39). The prognosis after migrainous infarction is reported to be more benign than after an infarct of another cause. Patients are likely to have a relatively favourable outcome with often only minor remaining deficits and no residual symptoms in 65% of patients (39).

Sometimes a migraine aura is mistaken for ischaemic stroke and patients are admitted to the hospital and treated with thrombolysis. Studies report migraine as the likely aetiology in 8–38% of stroke mimic cases. In total, around 40 such patients have been reported in the literature and in none of them has haemorrhagic complications occurred (45–48). Computed tomography (CT) perfusion abnormalities showing either hyperperfusion or hypoperfusion not reaching penumbra limits have been found in small series of such patients (49).

Intracerebral haemorrhage

An ICH is bleeding that occurs within the brain tissue (see also Chapter 10). When no large-vessel malformation is found it is often called primary or spontaneous ICH. Deep ICH is often due to small vessel disease caused by hypertension and/or diabetes, whereas lobar ICH is thought to be more often related to amyloid angiopathy. Headache is one of the main presenting symptoms of ICH and is reported in 34–57% of cases (20,50–52).

Analogous with ischaemic stroke, headache at ICH onset is more common in cerebellar and lobar haemorrhages than in deep haemorrhages. In multivariable analyses in 165 patients, female sex (OR 1.6), presence of meningeal signs (OR 2.3), cerebellar or lobar location of the ICH (OR 2.1), and transtentorial herniation (OR 1.8) were statistically significant predictors of headache at ICH onset (52). Surprisingly, these factors were more predictive of headache presence than haematoma location and the authors suggest that headache is more often related to activation of an anatomically distributed system in susceptible persons and to the presence of subarachnoid blood than to intracranial hypertension (52). Another study that included 189 patients with supratentorial ICH admitted within the first 12 hours of symptom onset found a relationship with several inflammatory markers. Patients with headache had a significantly higher frequency of history of infection, inflammation, and higher body temperature than patients presenting without headache (51). In addition, leukocyte count, erythrocyte sedimentation rate, mass effect on admission, and plasma concentrations of interleukin-6 and tumour necrosis factor-α were significantly higher in patients with headache. Headache was also associated with the residual cavity volume of the haemorrhage (51).

Headache in ICH has most often been described as tension-type headache, followed by a migraine phenotype (31). Compared to headache in ischaemic stroke, headache in ICH has approximately the same duration with a mean of 4 days but is significantly more incapacitating (30,31).

In the chronic stage after ICH, headache is also a frequently encountered problem. ICH survivors, who were asked in the second year after ICH for headaches before and after ICH by a headache questionnaire reported new headaches in 11% and ongoing headaches in 43%. Twenty-four patients (27%) never had headaches and in 17 (19%) previous headaches remitted after the haemorrhage (53). Remission of headaches seemed to be related to removal of headache precipitants such as alcohol use or possibly to structural or functional changes of the trigeminovascular system. Chronic post-ICH headaches were usually tension-type in phenotype and were significantly associated with depression (53).

Subarachnoid haemorrhage

A SAH is a bleeding in the subarachnoid space of the brain caused in 90% of cases by a ruptured aneurysm (aSAH). In approximately 10% of patients no aneurysm is found. When the blood is primarily located around the brainstem, a perimesencephalic SAH (PMH) is diagnosed, which most likely has a venous cause.

Patients with aSAH typically present with sudden thunderclap headache (see Chapter 34) and/or loss of consciousness combined with nausea, vomiting, and sometimes neurological symptoms. In approximately one-third of patients, headache is the single clinical symptom, whereas in < 1% of the patients, no headache occurs (54,55). Most of patients with aSAH without headache present with an acute confusional state (55). Headache in patients with aSAH usually starts instantaneously in 50% of patients and within 5 minutes in another 19% (56). In patients with PMH, headache developed almost instantaneously in 35%, and within 1–5 minutes in 35% (56). How long the headache generally lasts is less clear and therefore there is no clear cut-off point to rule out aSAH by headache duration. A headache duration of 1–2 weeks has been described, but some patients report disappearance of their headache the first hours after the start of the haemorrhage (57). Headache caused by aSAH is in general diffuse and extremely severe (57). It is unknown if the character of the headache differs between aSAH and PMH. Continuing headache in patients with aSAH during admission requires medical attention as it can be a sign of a developing hydrocephalus or treatment (drain)-related infection.

There is debate in the literature whether in some patients a warning leak occurs. A warning leak is assumed to be an episode of acute headache in the days or weeks just before rupture of an aneurysm caused by a sudden distention of the aneurysm or subintimal haemorrhage in the aneurysm wall (58). When a warning leak exists, it would give an opportunity to prevent aSAH by urgent treatment

of the aneurysm. However, it is likely that its association is at least partly based on recall bias (56).

In the chronic stage after SAH headache is also often encountered. In a long-term follow-up study of 610 patients with a clipped aneurysms after aSAH, 12% of patients reported chronic headaches after a mean follow-up period of 9 years (59).

Cerebral venous sinus thrombosis

CVST occurs when a blood clot forms in the brain's venous sinuses that prevents blood from draining out of the brain. CVST is a rare but serious cause of headache. Headache is the most common presenting symptom and is present in 70–90% patients (60–62). Headache seems to be less common in paediatric patients, where it was reported in only one-third of cases (63). In CVST patients presenting with headache, around 20% already had a previous history of headache, including migraine, tension headache, and cluster headache (63). Headache in patients with CVST is associated with other clinical symptoms as focal neurological deficits (36%), seizures (32%), and papilloedema (32%) (61). However, in 32% of patients with headache neurological examination was normal and 12–15% had headache as sole symptom (61). Diagnosis of CSVT is especially challenging in these cases and only imaging can reveal the cause for the headache (61,64). When CVST is suspected, contrast-enhanced MRI or CT venography is required to establish the diagnosis (65).

The presentation of headache in CVST is diverse and can mimic thunderclap headache (see Chapter 34), migraine, orthostatic headache, cluster headache, headache related to increased intracranial pressure, and diffuse tension-type headache. The duration of headache is 1–3 days in almost two-thirds of patients, 4–14 days in a quarter, and > 14 days in one-tenth of patients (63). The quality of headache most often is band-like (20%), followed by throbbing (9%), thunderclap (5%), or other (pounding, exploding, stabbing (20%)). The location of headache is reported to be unilateral in 37%, localized in 19%, and diffuse in 20%. There seems to be no association between headache and the presence of hydrocephalus or venous haemorrhages on imaging. Most patients had diffuse headache without any significant association to the presence of haemorrhage and location of thrombosis. One exception might be sigmoid sinus thrombosis, where 17 of 28 (61%) patients reported pain in the occipital and neck region (63).

The mechanism underlying headache occurrence in CVST is not well understood. Mechanisms that are proposed to play a role in headache pathogenesis are the stretching of sensory afferent nerve fibres in the dural venous sinuses, inflammation of sinus walls, raised intracranial pressure, and presence of SAH. The significant correlation between sigmoid sinus thrombosis and occipital pain is possibly related to inflammation and stretching of sigmoid sinus walls due to the thrombus (63). Chronicity of headache after CVST has been reported by a 1-year follow-up study, where 14% of the 624 patients reported severe headache (66).

Reversible cerebral vasoconstriction syndrome

RVCS is a condition characterized by one or more episodes of thunderclap headache (see Chapter 49). Patients were found to experience an average of 4–5 attacks occurring in a mean period of 1 week; attack duration varied from 5 minutes to 36 hours (67,68). While there can be other concomitant symptoms such as stroke or epileptic seizures, around three-quarters of patients experience headache as the only symptom. On imaging segmental constriction of vessels can be found, sometimes combined with cortical subarachnoid blood, cerebral ischaemia or ICH (67,69). Moderate headache persists between exacerbations. In a series of 191 patients with RCVS followed for a median of 78 months, 53% reported chronic/persistent headache of mild-to-moderate intensity that are distinct from the 'thunderclap' headaches at RCVS onset. The majority (88%) reported improvement in the severity of headache over time. The majority (97%) regain complete functional ability, but anxiety/depression are frequent, often aggravated by concomitant chronic headaches, and may be associated with lower quality of life (70). The underlying pathophysiology is still poorly understood, but it is probable that a transient disturbance of regulation of cerebrovascular tone plays a role (71).

Cervical artery dissection

Spontaneous CAD is a separation of the layers of the cervical artery wall and a frequently encountered cause of cerebral infarction, especially in young stroke patients (see also Chapter 10). Besides dizziness/vertigo and stroke, headache and neck pain are often encountered in patients with CAD and present in approximately 50% of patients (72). In around 10% of the patients headache is the only symptom (73). Other presentations include local manifestations such as Horner syndrome, cranial nerve palsies, tinnitus, or, more rarely, cranial root pathology. Patients with internal carotid artery (ICA) dissection more often present with headache but less often present with cervical pain. In addition, patients with dissections of the ICA have cerebral ischaemia less often than patients with vertebral artery disease (74). Of 20 patients with pain as the only symptom (12 with vertebral, three with ICA, and five with multiple dissections), six patients presented with headache, two with neck pain, and 12 with both. The onset of headache was progressive in six, acute in eight, and of a thunderclap nature in four. Headache was described as throbbing in 13 and constrictive in five patients. Pain was unilateral in 11 and bilateral in nine patients (73).

Migraine is more common among patients with CAD than patients without CAD. In a large series of 635 patients with CAD with stroke and 653 controls (patients with non-CAD stroke), migraine was found in 36% of patients with CAD versus in 27% of the controls (75). This difference was statistically significant. In particular, migraine without aura (MO) was more prevalent in patients with CAD (20% vs 11%) (75). In a meta-analysis including five case–control studies, MO almost doubled the risk of CAD (OR 2.06, 95%CI 1.21–3.10). The association with MA was less strong (OR 1.50, 95% CI 0.76–2.96) (76). The pathophysiology and the causality of the association between migraine and CAD remains to be elucidated. A recent genome-wide association study of CAD identified a significant association at the same index single nucleotide polymorphism (SNP) (rs9349379 in the *PHACTR1* locus) as is associated with migraine, indicating the potential for a shared genetic relationship between migraine and CAD (77). A positive migraine history did not affect the chance of ischaemia, the distribution of strokes, or the prognosis in patients with CAD (75).

Arteriovenous malformations

Arteriovenous malformations (AVMs) of the brain are abnormal direct connections between arteries and veins within the brain

parenchyma leading to shunting without a true capillary bed resulting in a nidus of tangled vessels. They are mostly detected in patients around the age of 30–40 years. Their exact prevalence in the general population is uncertain but is estimated to be around 0.1% (78). The relationship between AVMs and headache has been reported for a long time but remains controversial. Headache as symptom at detection of unruptured AVMs has been described in 25–56% of patients with occipital AVMs, but prospective data are lacking (79,80). In a large combined database of 1289 patients with AVM from three hospitals, chronic headache at the time of diagnosis was reported in 14% of cases (78). In a retrospective series of 37 patients with small occipital AVMs treated with radiosurgery, periodic headaches were found in 17 (46%) of the patients and seemed to occur more often with a larger nidus volume, tortuosity of the feeding artery, and cortical drainage with reflux in the superior sagittal sinus (81).

The most often described primary headache syndrome associated with AMVs is migraine, especially MA. In several series of patients with AVM, migraine was present in 19–23% of cases (80,81). Whether the relationship between migraine and AVMs is causal remains unclear, as migraine has a high prevalence in young, otherwise healthy adults, and especially in women. However, one study reported 58% of women with cerebral AVMs to have migraine (32% MA and 26% MO) (82). The number of women with MA in this study seems to be higher than expected in the general population.

In older studies, migraine is reported particularly in occipital, parietal, and temporal AVMs, and less in frontal and only rarely in central AVMs (83). In favour of a causal relationship are the findings of an observational study of 40 patients, where in all patients with occipital AVM the migraine symptoms occurred ipsilateral to the AVM lesion (80). In addition, after AVM treatment, migraine symptoms sometimes seem to improve (84,85). In a small series of 17 radiosurgically treated patients headaches resolved or improved in 12 (71%) of cases, including six of seven patients with migraine (81).

Where some report classic migraine histories according to the International Classification of Headache Disorders (ICHD)-2 criteria (80), others state that after careful review of the patient history most spells diagnosed as aura were atypical for migraine and some could rather be epileptic phenomenon (86). In most patients with AVM with migraine no family history for migraine is present (81). Other types of primary headache syndromes that have been described in patients with AVMs are cluster headache, chronic paroxysmal hemicranias, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) (87–90). For cluster headache improvement of symptoms after AVM treatment have been described in one case report (91).

The exact yield of screening for AVMs in patients with MA in general or in case of atypical symptoms is unknown. Imaging of the brain should be strongly considered in patients with strictly unilateral symptoms of migraine, late onset of migraine, change in attack frequency, or neurological symptoms, including epileptic seizures.

The pathophysiology behind the association between headache and AVMs is not clear. It has been suggested that the high frequency of headache and migrainous symptoms in AVMs supplied by the posterior cerebral artery suggests a particular sensitivity in this arterial system. For AVMs in the occipital lobe, a link with spreading depolarization (SD) has been described, as this area of the brain is more susceptible to this phenomenon, which is the presumed underlying mechanism of migraine aura (80). The headaches may be related to involvement of the dural arterial system to the AVM. Dural supply to the AVM was found to be present more frequently in patients with headache than in those without headache. However, headache also occurred in the majority of patients without an identifiable dural arterial supply to the AVM (79).

Unruptured aneurysms

Whether unruptured aneurysms can be a cause of headache is unknown. Most unruptured intracranial aneurysms are thought to be asymptomatic lesions. However, several case reports associate unruptured aneurysms with headaches sometimes in combination with cerebrospinal fluid lymphocytosis (92,93). In addition, a positive effect of aneurysm treatment on headache symptoms has been suggested in single cases and small-size studies. In one study that included 72 elderly patients, of whom 72% reported headache before treatment, three-quarters reported improvement of headache after endovascular treatment (94). A prospective study of 44 patients (38 coiled, five clipped, and three treated with liquid embolic infusion) also found a decrease in 90-day headache frequency. Headache frequency was reduced in 68% of patients, but 9% of patients had new or worsening headaches following treatment. Pretreatment migraine, more severe pretreatment headaches, higher pretreatment anxiety and stent-assisted aneurysm coiling were associated with absence headache improvement (95). Two other studies reported headache improvement in > 90% of cases (96). No differences were found between the surgical and endovascular group (97).

Headache in the first days after aneurysm treatment and exacerbation of existing headache have been found in other studies (98,99). More than half of 90 patients treated with coiling experienced headache in the first hours after the procedure. All headaches resolved within an average of 3 days. No hypertension history and a coil packing attenuation of > 25% were suggested risk factors of headache development. After certain special endovascular treatments, such as flow-diverting stents and bioactive coils, peri-aneurysmal brain inflammation and oedema have been found (100,101). It is unclear if these findings are related to the occurrence of postprocedural headache.

Cavernomas

Cavernous hemangiomas or cavernomas are blood-filled, enlarged, immature capillaries lined with a single layer of endothelial cells without intervening neural tissue, ranging in size from a few millimetres to several centimetres (102). The prevalence is around 1 in 100,000 in children and around 18 in 1,000,000 in adults (103).

There are few clinical and demographic studies on cavernomas with large sample sizes. Headache as initial presentation is reported in 31–65% of patients (104,105). Other frequent symptoms are epileptic seizures or intracranial haemorrhage. Clinical presentation in children is different, where headache at presentation is reported less often (3–18%) and presentation with ICH is more prevalent (102,106). In a prospective follow-up study of 35 patients, 11 had headache at initial presentation. During follow-up chronic headache developed in 19 of 35 patients, and all patients developed seizures (104).

A number of case studies link cavernomas with the occurrence of migraine (107–109). In one study the disappearance of new-onset

migraine was described after the removal of a cavernoma in the left temporo-occipital lobe (107). In other case studies, chronic migraine and chronic occipital neuralgia was linked to cavernomas in the brainstem, suggesting a role for the trigeminocervical system and the contralateral midbrain periaqueductal grey matter (108).

Cerebral angiitis

Headache is a common manifestation of primary angiitis of the central nervous system (PACNS) or secondary forms of vasculitis, caused by systemic vasculitides. PACNS is a rare disease affecting both medium- and small-sized vessels, with an estimated annual incidence of 2:1,000,000 (110). The mean age of onset is 50 years, and men are affected twice as often as women (111). There is no precise test or marker that is specific to the disease, and high clinical suspicion coupled with thorough investigations are needed to exclude mimics. One important mimic of PACNS is RVCS, as this disorder has the same radiological features and in both diseases headache is the main symptom of clinical presentation. In contrast with RVCS, where headache is reported in all cases and characterized by thunderclap onset, in PACNS headache occurs in 57–63% of cases and is described as insidious-onset subacute headache. Thunderclap headache was not present in any of the patients (110,112). Prompt recognition of primary or secondary vasculitis is needed to not only treat headache symptoms, but also to prevent secondary symptoms such as stroke, seizures, and encephalopathy.

The nature of headache in vasculitis is not well described. A stabbing nature of the headache has been reported to be related with autoimmune disorders via neuroinflammation (113). Presentation as migraine has been reported in a paediatric case (114). In the case of temporal located pain, giant cell arthritis (GCA) should be suspected. GCA is the most frequent form of vasculitis in patients older than 50 years of age, with a prevalence of 15–30/10,000 (115). In 50% of patients with GCA headache is the initial symptom, and eventually it occurs in 90% of patients (116). The headache in GCA can be accompanied by jaw claudication. Other neurological symptoms include visual problems, such as diplopia, flicker scotoma, and amaurosis fugax, with blindness or stroke as a dreaded complication (110). Headache in GCA can take many forms, and can present as migraine, cluster headache, tension headache, and even thunderclap headache (116,117).

Genetic cerebral angiopathies

The close relationship between migraine and stroke becomes clear in several monogenetic disorders were migraine and cerebrovascular symptoms occur together (see also Chapter 8). Investigation of these monogenetic diseases such as familial hemiplegic migraine (FHM), cerebral autosomal dominant arteriopathy with subcortical infarct and leukoencephalopathy (CADASIL), retinal vasculopathy with cerebral leukodystrophy and systemic manifestations (RVCL-S), and mitochondrial myopathy with encephalopathy, lactate acidosis, and stroke (MELAS) offers a unique opportunity to increase understanding of the pathophysiology behind the connection between migraine and stroke. FHM is an autosomal dominant disease in which MA is the key symptom. The migraine symptoms are typically accompanied by the gradual onset of neurological deficits, mostly hemiparesis, which can last for hours to weeks. An attack resembles a stroke, but, unlike a stroke, it resolves in time. Other associated symptoms are ataxia and coma. FHM is caused by mutations in several genes: *CACNA1A* (FHM1), *ATP1A2* (FHM2), and SCN1A (FHM3).

CADASIL is a disease caused by a mutation in *NOTCH3* that is characterized by dementia, white matter lesions, and lacunar infarcts. Migraine, most often with aura, is present in 20–40% of the cases and is often the presenting event. Migraine auras are often prolonged, atypical, or associated with confusional episodes (118). However, in a study of 55 patients with CADASIL with a R544C mutation and an overall headache prevalence of 45%, the majority (88%) of patients had tension-type headache (119).

In contrast to FHM and CADASIL, RVCL-S is mostly associated with MO. RVCL is caused by a mutation in *TREX1*. MELAS is a disease that affects many parts of the body but mainly the central nervous system and the muscles. It is caused by mutations in the genes in mitochondrial DNA. In MELAS, migraine-like headache episodes can be followed by acute neurological symptoms.

Headache as a prognostic factor for vascular disorders

Headache at stroke onset may not be just innocent bystander but could, because of an associated different underlying pathophysiology, influence short- and long-term outcome after stroke. In this section the studies on headache and prognosis in ischaemic and haemorrhagic stroke are described. Less is known about the prognostic role of headache in sinus thrombosis, SAH, vascular malformations, RVCS, and angiitis.

Short-term outcome

Five studies that investigated headache and short-term outcome found contrasting results regarding the relationship between concomitant headache and stroke outcome. (15,16,20,22,26). In the first prospective, community-based cohort of both haemorrhagic and ischaemic stroke patients, 241 of 867 (28%) patients had headache in relation to stroke onset. There was no correlation between headache and mortality and stroke outcome at time of discharge, as measured with the Scandinavian Stroke Scale (16,120). In the second study, data on headache were available for 1391 patients, of whom 1185 had an ischaemic stroke and 201 had an ICH. Headache was found in 18.2% of patients (46.3% of ICH and 13.5% of ischaemic stroke patients) and was associated with a higher 30-day mortality in ICH (HR 2.09, 95% CI 1.18–3.71) but not in ischaemic stroke (HR 1.01, 95% CI 0.53–1.92) (20). In the third study, no differences in neurological or functional outcome 6 months after discharge were detected between 145 lacunar ischaemic stroke patients with and without headache within the first 72 hours after symptom onset (26). In the fourth study, including 11,523 participants in the Taiwan Stroke Registry, patients with onset headache (7.4% of the population) had a lower frequency of stroke evolution, a greater improvement in National Institutes of Health Stroke Scale score on discharge, a higher mean Barthel index, and a lower frequency of a modified Rankin Scale (mRS) score > 2 (15). There was also a trend for better functional outcome at 3 and 6 months in this follow-up (15). The fifth study, which included 284 ischaemic stroke patients, found no difference in mRS score > 2 at the 3-month follow-up in patients with onset headache (38% of the population) versus patients without (22).

Long-term outcome

In a long-term follow-up study of ischaemic stroke patients, concomitant headache appeared to result in a better outcome with fewer recurrent vascular events and a lower overall death rate. In this study, 2473 participants of the Dutch TIA trial with a TIA or minor stroke of non-cardioembolic origin, were followed over a median time of 14.1 years (29). Onset headache was present in 17% of this population, was more prevalent in women, and more often associated with lesions involving the cortical and posterior circulation. Patients with headache at stroke onset had an adjusted HR of 0.83 (95% CI 0.71–0.97) for new vascular events during follow-up. For cardiac events the adjusted HR was 0.88 (95% CI 0.67–1.14), and for cerebral events the HR was 0.97 (95% CI 0.76–1.24). Participants with headache were at lower risk of vascular death (adjusted HR 0.73, 95% CI 0.61–0.87).

Migraine, spreading depolarizations, and outcome after stroke

SDs are presumed to be the underlying mechanism of a migraine aura and are characterized by slowly spreading waves of depolarization (temporary loss of function) of brain cells (121). In healthy brain this mechanism is relatively benign, but SDs can be harmful in damaged brain tissue (121). Migraineurs with aura are probably more susceptible to SDs. As SDs are thought to have a detrimental effect on recovery of cerebral ischaemia one could expect patients with MA to be at risk for a poorer outcome after stroke. FHM type 1 mice harbouring the *CACNA1* mutation are more susceptible to SDs and were shown to have larger strokes and a higher mortality after middle cerebral artery occlusion than wild-type mice (122). However, in a large prospective cohort of 27,852 women enrolled in the Women's Health Study a relatively good functional outcome was found in female migraineurs (123). During a mean follow-up of 13.5 years, 398 TIAs and 345 ischaemic strokes occurred in this cohort of women without a history of cardiovascular disease, cancer, or other major illnesses and an age of ≤ 45 years at baseline. Compared with women without a history of migraine and who did not experience a TIA or stroke, women who reported active MA had an adjusted relative risk of 1.56 (95% CI 1.03–2.36) for TIA, 2.33 (95% CI 1.37–3.97) for stroke with a good outcome (mRS 124 0–1) (124), 0.82 (95% CI 0.30–2.24) for stroke with a moderate outcome (mRS 2–3), and 1.18 (95% CI 0.28–4.97) for stroke with a poor outcome (mRS 4–6). The risk of any of these outcomes was not significantly higher in women who experienced MO or who had a past history of migraine (123).

Pathophysiology of headache related to neurovascular disorders

The underlying pathophysiological mechanisms behind headache in vascular diseases are, in general, poorly understood. In this section the pathophysiology of headache as risk factor, symptom, and prognostic factor is summarized.

Pathophysiology of headache as risk factor

A number of factors may underlie the occurrence of ischaemic stroke in migraineurs. It is important to distinguish the timing of stroke in those with migraine, as the underlying pathophysiology may differ. Stroke may occur during or completely separately from a migraine attack. The occurrence of stroke during a migraine attack is known as migrainous infarction. This is a very rare syndrome. Even in those cases that meet the ICHD-3 criteria for migrainous infarction, cerebral ischaemia can precipitate cortical spreading depression (CSD) and aura symptoms, and, in some cases, the migraine aura is likely symptomatic of cerebral ischaemia rather than the ischaemia and infarction being secondary to events that occur during the migraine attack. Nevertheless, several physiological events during a migraine attack, particularly with aura, may increase the risk of ischaemic stroke in a vulnerable individual. CSD is associated with a profound metabolic derangement characterized by a significant increase in the consumption of high-energy phosphates, glucose, and oxygen, while nutrient substrate delivery is compromised by metabolic flow uncoupling and a reduction in cerebral blood flow (125–128). While not usually sufficient in humans to result in irreversible cerebral injury, the combination of these physiological changes and other factors shown to be present in those with MA, such endothelial dysfunction, elevated circulating procoagulants, and inflammatory cytokines, especially in the setting of oral contraceptive use or environmental factors such as dehydration and elevated blood viscosity, may be sufficient to result in cerebral infarction (129,130).

The underlying mechanism(s) by which migraine increases the risk of ischaemic stroke independently of migraine attacks (migrainous infarction) is likely multifactorial. Migraine is associated with well-established and emerging cardiovascular and cerebrovascular risk factors, including obesity (131,132), patent foramen ovale (133), increased tobacco and exogenous hormone use (13,134), cervical carotid artery dissection (76), and elevated Framingham risk scores, versus non-migraineurs (5,135).

Endothelial dysfunction has also been considered to be a potentially important pathogenetic factor underlying the increased risk of ischaemic stroke in those with MA (129).

MA has been associated with Sneddon syndrome, a disorder characterized by endothelial dysfunction. Migraine is also associated with elevated levels of biomarkers of endothelial dysfunction, including tissue plasminogen activator, high-sensitivity C-reactive protein, von Willebrand factor, vascular endothelial growth factor and nitric oxide metabolites, lower levels of endothelial repair (progenitor) cells, and elevated levels of procoagulants, including prothrombin fragment 1.2 (136–139).

An emerging body of evidence also supports an association between migraine and inherited risk factors for venous thromboembolism and vascular disease. There is an increased risk of MA in carriers of factor V Leiden or factor II G2021 mutations (140). Individuals with methylenetetrahydrofolate reductase 677 TT genotype appears to increase the risk of MA and this combination has been shown to increase the risk of ischaemic stroke (OR 1.81, 95% CI 1.02–3.22; HR 4.19, 95% CI 1.38–12.74) (141,142). A recent meta-analysis of 22 genome-wide association studies that included data from 59,674 patients with migraine and 316,078 controls collected from six tertiary headache clinics and 27 population-based cohorts identified 44 independent SNPs significantly associated with migraine risk that mapped to 38 distinct genomic loci, including 28 loci not previously reported and a locus identified on chromosome X—a finding not previously reported. Several of the identified genes (*PHACTR1, TGFBR2, LRP1, PRDM16, RNF213, JAG1, HEY2, GJA1*,

and *ARMS2*) have previously been associated with vascular disease or are involved in smooth muscle contractility and regulation of vascular tone (*MRVI1, GJA1, SLC24A3*, and *NRP1*). This seminal work provides evidence that migraine-associated genes are involved in both arterial and smooth muscle function and represents both the potential for the vasculature to be a trigger for migraine, as well as underscoring a potential genetic predisposition to ischaemic stroke in migraineurs (143).

Pathophysiology of headache as symptom

Headache as a symptom of stroke is generally thought to be due to stimulation of cerebral pain regulation systems. Intracranial nociceptive structures are the meninges and blood vessels. These structures are innervated by the ophthalmic branch of the trigeminal nerve; afferent fibres pass through the trigeminal ganglion and synapse on second-order neurons in the trigeminocervical complex. These neurons, in turn, project through the quintothalamic tract (144). Stimulation of sensory afferents of the trigeminovascular system is increasingly recognized as a very important pain-regulating mechanism. The trigeminovascular system can be triggered in several ways. As described previously in this chapter, one detrimental mechanism that is indirectly able to stimulate the system is CSD (145,146). The posterior circulation is more densely innervated by the trigeminovascular system than the anterior circulation. This might explain, in part, why headache more often occurs in vertebrobasilar strokes. Other pain-regulating centres may also be involved. Stroke-related pain has been linked to lesions in the thalamus (147,148). Interestingly, stroke-associated headache occurs more often in patients with a history of headache. This seems to be the case for different types of headache, such as migraine and tension-type headache. It has been suggested that in these patients pain-sensitive mechanisms are reactivated, triggered by their stroke. For migraineurs, a higher susceptibility for SD might play a role in reactivation of prestroke headache.

In addition to the pain-regulation systems, more generalized mechanisms are activated in the brain during and after stroke. Raised intracranial pressure is a known cause of headache. The relation that was found in headache and lesion size in ischaemic stroke patients with size of haematoma cavity and signs of herniation in patients with ICH point in this direction. In one study headache was more severe with movement and coughing (31). The role of lesion-related oedema is not clear. Headache at ICH onset was associated with cerebral inflammation (51). For ischaemic stroke, evidence for an association between inflammation and headache is lacking. Some studies have found a higher frequency of headache in patients with high blood pressure on admission (18). This may suggest a role for a disturbance in autoregulation. The dysfunction of autoregulation especially affects the posterior regions of the brain. This is emphasized by the fact that headache is also frequently encountered in hypertension-related vasculopathies like posterior reversible encephalopathy syndrome and cerebral hyperperfusion syndrome after carotid endarterectomy (149,150).

Local vascular structures and vascular drainage patterns are also linked to headache occurrence, especially in patients with AVM and CVST. In patients with AVM, headache was associated with a larger nidus volume, tortuous change of feeding artery, cortical drainage with reflux in the superior saggital sinus, and dural arterial supply to the AVM (79,81). In one small CVST study, the majority of patients with sigmoid sinus thrombosis reported pain in the occipital and neck region (63). However, large studies on local vascular structures and stroke headache are limited and therefore these data should be interpreted with caution. The advent of new non-invasive imaging techniques such as CT angiography and MR angiography and perfusion offer an opportunity to gain more insight in the relation between local vascular structures and stroke-related headache.

Pathophysiology of headache as prognostic factor

As described herein, there are conflicting results on the association between headache and short-term outcome in ischaemic stroke. For haemorrhagic stroke this relationship seems to be more robust. As headache in ICH is related to haemorrhage size, posterior location, and inflammation, these factors might contribute to a relatively poor outcome. SDs are supposed to have a detrimental effect on recovery of cerebral ischaemia in stroke patients in general (not only patients with a history of migraine) (121). In animal experiments, SDs in injured brain resulted in hypoperfusion and aggravation of ischaemia (122). Recently, it was shown that SDs occur and play a detrimental role in the penumbra of patients with large middle cerebral artery infarctions (145). In addition, in a small series of patients with SAH, SDs were found to be related to the occurrence of delayed cerebral ischaemia (DCI) (151). Future research should further determine the exact role of SD in outcome after stroke in humans.

The more benign long-term vascular prognosis in patients with headache at presentation of ischaemic stroke might point to a different pathophysiology behind the stroke or might be caused by a difference in associated vascular risk factors in stroke patients with and without headache. Certain subtypes of stroke present more often with headache than others. These stroke subtypes might have more benign vascular prognoses, possibly because they are not directly related to atherosclerosis. Arterial dissections and RCVS are examples of diseases associated with headache and a better long-term outcome (152,153). There might also be a relation between headache at presentation and cardiovascular risk factors. Headache at ischaemic stroke onset is more often found in relatively young patients without cardiovascular risk factors such as hypertension. This better cardiovascular risk profile in patients with headache might explain the more benign long-term prognosis, but further research on this topic is needed.

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38

Headache attributed to spontaneous intracranial hypotension

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Introduction

Cerebrospinal fluid (CSF) leaks can occur spontaneously or after a dural puncture. While both types of CSF leak lead to a reduction in CSF volume, spontaneous leaks can differ from dural puncture leaks in terms of clinical presentation, location of the leak, response to blood patch, and overall prognosis. Spontaneous intracranial hypotension (SIH) was defined in 1997 as a triad of postural headache, low CSF pressure, and imaging abnormalities. However, since then, it has become apparent that not all patients display an orthostatic headache, especially as time goes on, not all patients have low CSF opening pressures on testing, and not all patients clearly show signs of CSF leak on routine imaging. Therefore, the definition has become broader over time but still lacks high sensitivity. The latest version of the International Classification of Headache Disorders (ICHD-3), defines SIH as headache which has developed in temporal relation to the CSF leakage, or has led to its discovery, with either low CSF pressure (< 60 mm water) and/or evidence of CSF leakage on imaging (1).

Almost all cases of SIH occur at the level of the spine rather than the cribiform plate or skull base (2). With the advent of magnetic resonance imaging (MRI) and other advanced imaging studies, it has become much easier to detect SIH and this has led to the discovery that symptoms can vary considerably. In this chapter, we will review the epidemiology, clinical features, pathophysiology, investigations, treatment options, and prognosis of SIH.

Epidemiology

The true incidence and prevalence of CSF leaks are unknown. Although some report an incidence of 2–5 cases per 100,000 people per year, CSF leaks are considered to be underdiagnosed (3,4). Women appear to be affected more than men, with a female-to-male ratio of 2:1 (5). SIH has been reported in 2-year-old to 86-year-old patients, with a peak incidence occurring between 35 and 42 years of age (4–8).

Pathophysiology

In the vast majority of cases, SIH results from spontaneous CSF leaks. Most of these leaks occur at the level of the spine, commonly at the cervico-thoracic junction or the thoracic region (9–11). Rarely, a leak can occur at the skull base. These leaks can occur as a result of defects in the cribiform plate, the sphenoid and frontal sinuses, the ethmoid roof, the sella, or the temporal bone (9).

Although there is much variability with regard to clinical presentation and findings on imaging in patients with SIH, the key pathogenetic factor is loss of CSF volume (11,12). In many cases of SIH, the exact underlying cause for the leak remains unknown, but the aetiology and pathogenesis of this condition are felt to be multifactorial (10).

The presence of a connective tissue disorder is a risk factor for the development of SIH. Among these, Ehlers–Danlos syndrome type II, Marfan syndrome, and autosomal dominant polycystic kidney disease are the conditions most likely to be associated with CSF leaks (10). These patients appear to have a weakness of the connective tissue matrix within the dural sac. In these cases, CSF leaks can occur spontaneously, or a trivial trauma, such as coughing or lifting, may be sufficient to cause a dural tear leading to a CSF leak (10,11). Some patients with connective tissue disorders also have ectatic dural sacs, meningeal diverticula, and dilated nerve root sleeves (10,12). Familial cases of SIH have been described, mainly in patients with underlying connective tissue disorders (10).

Spondolytic spurs and herniated discs can also be a causative factor in the creation of CSF leaks (10,11). Occasionally, congenital bony spurs can also be found. At the time of surgery, many other abnormalities of the dura can be found, such as dural holes or rents, or even complete absence of the dura (10).

The symptoms of SIH can be explained by the loss of CSF volume and the Monro–Kellie hypothesis (11,12). This hypothesis states that with an intact skull, the sum of the volume of brain, CSF, and blood is constant (11,12). Therefore, if there is loss of CSF, other components in this equation must compensate for that loss. As a result, the blood component tends to increase, resulting in venous engorgement and

pituitary hyperaemia. The meningeal venous hyperaemia leads to pachymeningeal enhancement. Subdural fluid collections are also compensatory (11,12).

The headache is felt to be as a result of sagging of the brain and traction of the pain-sensitive structures (9,11). Engorgement of venous structures may also contribute to the pain experienced by patients (9,12). The postural nature of the headache may be related to worsening of CSF hypotension due to gravitational pull and from an increase in the sagging of the brain and traction of the pain-sensitive structures when upright (9).

Cranial nerve deficits, including vestibulocochlear dysfunction, are felt to be related to traction and compression of the corresponding nerves at the level of the brainstem (9,11). Alterations in the pressure of the perilymph in the inner ear may also be responsible for altered hearing and tinnitus (9). Other clinical features also seem to relate to traction of other structures in the brain, such as the pituitary stalk or mesencephalon (11). However, one must keep in mind that these explanations have not been proven.

Another postulation for the headache is that there may be an altered distribution of craniospinal elasticity. This may occur as a result of spinal loss of CSF leading to spinal dural sac collapse and increased compliance of the lower spinal CSF space (10).

In 2010, an Italian group proposed a novel speculative pathophysiological hypothesis for the cause of SIH (13). They proposed that the underlying pathology in SIH is not a primary loss of CSF from a dural tear, but a loss of CSF into the epidural space as compensation for negative pressure within the inferior vena cava (IVC). They believe that negative pressure within the IVC will result in over-drainage of venous blood from the spinal epidural venous plexus, resulting in a modification of epidural gradients (13). Franzini et al. (13) suggested that it is this modification that results in CSF leakage into the epidural space. However, it is unclear how the negative pressure in the IVC becomes significantly low enough to cause such a phenomenon. The authors do not provide a clear explanation for this. Their proposal has not been substantiated by other groups and remains entirely speculative.

Most recently, the current understanding of SIH pathogenesis holds that the symptoms are related to loss of intracranial CSF volume, rather than strictly a reduction in pressure (14). Many patients with SIH exhibit normal opening pressures. Perhaps this is related to the compensatory mechanisms described earlier. Hence, this compensation may, in turn, normalize the CSF opening pressure. What may lead to loss of CSF volume? This is felt to occur by three major aetiologies in the spine: (i) leaks secondary to dural weakness in the area of the nerve root sleeves/meningeal diverticula; (ii) ventral dural tears associated with degenerative disc disease/osteophytes/disc herniations; and (iii) CSF venous fistulas (14). The CSF venous fistula has recently been described and represents a direct connection between a paraspinal vein and CSF within the subarachnoid space.

Clinical manifestations

ICHD-3 defines SIH as a headache that has developed in temporal relation to low CSF pressure or CSF leakage, or has led to its discovery, along with the presence of low CSF pressure (< 60 mm CSF) and/or evidence of CSF leakage on imaging (**Box 38.1**) (1). Prior to the publication of the ICHD-3 criteria, in 2011 Schievink et al. (15) also proposed similar diagnostic criteria for headache due to SIH (**Box 38.2**) (15).

Box 38.1 ICHD-3 criteria for headache attributed to spontaneous intracranial hypotension

- **A** Any headache fulfilling criterion C.
- **B** Low cerebrospinal fluid (CSF) pressure (< 60 mm CSF) and/or evidence of CSF leakage on imaging.
- **C** Headache has developed in temporal relation to the low CSF pressure or CSF leakage, or has led to its discovery.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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The most common clinical manifestation of SIH is an orthostatic headache, or a headache that is present when upright and improves when supine (11,12,16,17), and this feature is experienced by > 95% of patients (18). Because SIH can have a sudden onset in 15% of cases, it also remains in the differential diagnosis of thunderclap headache (19–21). The pain is often described as throbbing, dull, or a pressure sensation, which can be severe and varied in location. Some patients feel the headache is holocephalic, and others cite specific regions, most often the occiput or subocciput region, as experiencing the most intense pain. Classically, the headache is expected to improve within 15–30 minutes of being supine, but, in reality, this can vary considerably (22,23). If SIH is left untreated, the positional component can diminish over time and it can simply be reported as a chronic daily headache and often mimic chronic migraine, chronic tension-type headache, or cervicogenic headache.

In some cases, the diagnosis can be challenging because the headache may lack the characteristic orthostatic component from the start. There are reports of patients presenting with Valsalva-induced or exercise-related headache, paradoxical headaches in which the pain is present when supine and improved when upright, headaches that lack obvious orthostatic features but instead the pain comes on later in the day (suggesting a subtle orthostatic component, as it comes on after an individual has been upright for a prolonged period of time), a new daily persistent headache phenotype, or even intermittent headaches that can be associated with intermittent CSF leaks (24–26). The presentation of a non-orthostatic headache with CSF leak may be due to a compensatory response with a normal physiological reaction to the CSF leak (27).

Box 38.2 Diagnostic criteria for headache due to spontaneous intracranial hypotension

- **A** Orthostatic headache.
- **B** The presence of *at least one* of the following:
  - **1** Low opening pressure (≤60 mm H_2O)
  - **2** Sustained improvement of symptoms after epidural blood patching
  - **3** Demonstration of an active spinal cerebrospinal fluid leak
  - **4** Cranial magnetic resonance imaging changes of intracranial hypotension (e.g. brain sagging or pachymeningeal enhancement)
- **C** No recent history of dural puncture.
- **D** Not attributable to another disorder.

Reproduced from *Headache*, 51, Schievink WI, Dodick DW, Mokri B, Silberstein S, Bousser MG, Goadsby PJ. Diagnostic criteria for headache due to spontaneous intracranial hypotension: a perspective, pp. 1442–1444. Copyright (2011) with permission from John Wiley and Sons.

A minority of patients lack headache altogether, and it is the other symptoms that lead to the discovery of the CSF leak. Owing to meningeal irritation, > 50% of patients experience posterior neck pain and stiffness with nausea, photophobia, and phonophobia. Vestibulocochlear symptoms, such as changes in hearing (echoing, under water sensation), tinnitus, ear fullness, and dizziness/vertigo, may be orthostatic and are the most common cranial nerve symptoms (28,29). Stretching of the vestibulocochlear nerve or abnormal CSF pressure to that of perilymph fluid are possible reasons for these symptoms (30).

Visual blurring; visual field defects; diplopia; facial numbness or facial pain; facial weakness or spasm; parkinsonism, including tremor and chorea; ataxia; and dementia have been rarely reported (31–34). Interestingly, the presence of diplopia with headache had a positive predictive value of 91%, while the presence of diplopia together with the absence of limb numbness had a positive predictive value of diagnosing a CSF leak in 95% (35).

In some patients, distortion of the pituitary stalk may lead to hyperprolactinaemia and galactorrhoea (36). Rarely, severe brain displacement may result in diencephalic herniation with decreased level of consciousness, encephalopathy, and even coma (37–39).

Spinal manifestations are uncommon; however, 6% of patients experience spinal symptoms/signs such as interscapular pain, local back pain at leak site, quadriparesis, and radicular symptoms (40). Spinal venous plexus engorgement may be the mechanism of the radiculopathy and myelopathy (41). The spinal manifestations are usually not positional, but instead thought be to related to mass effect from an extradural CSF collection (40).

It is important to keep in mind that features of SIH can be found incidentally on MRI without symptoms (42). Furthermore, orthostatic headaches may also occur in orthostatic hypotension, postural orthostatic tachycardia syndrome with excessive increase in heart rate when standing, vasovagal syncope, or even migraine, and this differential should be considered in patients with orthostatic headache and normal MRI of the brain (43,44). Cervicogenic headache can at times present with an orthostatic component as well (14,45). Other less common headaches that may be positional in nature include headaches associated with diabetes insipidus and post-decompression surgery for Chiari malformations (45,46).

Investigations

Over the years, many different diagnostic investigations have been used in patients with SIH. This section will review the pros, cons, and results of the various investigations, and then recommend an investigative algorithm based on the currently available evidence.

Lumbar puncture

A lumbar puncture and CSF analysis can be performed, but the results may be normal and the dural puncture itself may worsen the leak and subsequent intracranial hypotension (Table 38.1) (47). Although the opening pressure is sometimes low, it is in many cases within normal limits. Even in the same patient, variable opening pressures may be recorded at different time points, depending on the rate of flow of the leak (47). A retrospective case series that reviewed 106 patients with SIH showed that 61% of the patients had a CSF opening pressure between 6 and 20 cm water, and only 34% had a pressure ≤ 6 cm water (48). A few factors associated with increased pressure included abdominal circumference, symptom duration, and a normal MRI of the brain. This paper, in addition to others, indicates that a normal CSF opening pressure can occur often, and therefore the absence of a low CSF opening pressure should not exclude the diagnosis of SIH.

Table 38.1 Lumbar puncture and cerebrospinal fluid analysis in spontaneous intracranial hypotension.

Opening pressure	Typically low, but may be normal or may vary depending on the flow rate of the leak (44)
Colour	Typically clear, but may be xanthochromic or blood-tinged in the setting of a traumatic tap
White blood cells	May be normal or elevated (typically ~ 50 cells/mm^2) (45,46).
Red blood cells	May be normal or slightly elevated in the setting of a traumatic tap
Protein	May be normal or high (typically < 100 mg/dl)
Glucose	Normal
Gram stain	Negative
Cytology	Normal

The CSF is typically clear, but may be xanthochromic or blood-tinged in the setting of a traumatic tap (12). Traumatic taps are common in SIH, most likely due to the low opening pressure and/or engorgement of the epidural venous plexus (12). The erythrocyte count is typically normal, but can be elevated, usually in the setting of a traumatic tap (12). The leukocyte count is typically normal. However, a lymphocytic pleocytosis, ranging from 50 to 200 cells/mm^2, has been reported in the literature (49,50). The protein concentration can be normal or high; values > 100 mg/dl, have been reported but are rare (47). The glucose concentration, Gram stain, and cytology are always normal (12).

Radioisotope cisternography

Radioisotope cisternography may identify the presence of a CSF leak, but it rarely identifies the exact site of the leak. Radioisotope cisternography involves the intrathecal injection of a radioisotope, indium-111, followed by sequential scanning at intervals up to 24 or even 48 hours. Typically, at the 24-hour mark, radioactivity should be detected over the cerebral convexities (51–53). A CSF leak is suspected in the absence of radioactivity over the cerebral convexities at 24 hours. This is the most common abnormality that is seen on radioisotope cisternography in SIH (12). In addition, the early appearance of radioactivity in the kidneys and urinary bladder suggests that the intrathecally introduced radioisotope has leaked out of intrathecal space, entered the systemic circulation, been filtered by the kidneys, and appeared prematurely in the urinary bladder. However, false positives can occur via the extravasation of the radioisotope through the dural puncture, which would lead to early activity present in the urinary bladder. A CSF venous fistula can also contribute to the early appearance of the radioisotope within the urinary bladder. It is possible, but less common, that paradural activity may point to the level or approximate site of the leak. However, the accumulation of the radioisotope within meningeal diverticula or dilated nerve root sleeves may appear as paradural activity (12). In addition, inadvertent injection of the radioisotope extradurally

may appear as a collection of paradural activity. Myelography can differentiate between these possibilities. In suspected SIH, radioisotope cisternography may indicate the likelihood that a CSF leak is present; however, it is unlikely to indicate the site of the leak and it involves a dural puncture. Typically, in cases where radioisotope cisternography results suggest the presence of a CSF leak, a myelographic study is needed to confirm the presence of the leak and location prior to treatment.

Computed tomography of the head

A non-contrast computed tomography (CT) scan of the head is typically of limited value; however, it may show the presence of subdural fluid collections (12).

MRI of the brain and spine

MRI of the brain and spine can be very useful for the diagnosis of SIH and a spinal CSF leak. For the evaluation of SIH, an MRI of the brain with and without gadolinium contrast including T1-weighted midline sagittal views, as well as gadolinium enhanced T1-weighted coronal views through the sella and pituitary, are necessary (12). Common abnormalities on MRI of the brain with and without contrast in the setting of SIH include diffuse pachymeningeal enhancement without abnormal leptomeningeal enhancement, sagging of the brain with descent of the brainstem, engorgement of the venous structures, pituitary hyperaemia, and subdural fluid collections (11,12). A mnemonic has been proposed to remember the major MRI brain abnormalities present in SIH—SEEPS (**Box 38.3**) (4). Diffuse pachymeningeal enhancement is the most common MRI brain abnormality seen in SIH; however, it can be absent in some patients (54,55).

Other signs on MRI brain in SIH include the venous distension sign, which assesses the inferior margin of the midportion of the dominant transverse sinus. Normally, on T1-weighted sagittal views, this margin shows a concave or straight configuration, while in SIH it usually assumes a distended convex configuration (the venous distension sign). In one study, the sensitivity of the venous distension sign for the diagnosis of SIH was found to be 94%; specificity was also 94% (56). The 'venous hinge' sign: reduction of the angle between the vein of Galen and internal cerebral vein, which returns to baseline after treatment, has also been reported (57). The mamillopontine distance and the pontomesencephalic angle have recently been described as additional quantitative methods to aid in the diagnosis of SIH (58). The sensitivity and specificity of these measures is lower than that of the venous distension sign. Dural thickening of the internal auditory canal has also been described (59).

Novel orbital findings have also been described recently on routine brain MRI scans. Compared to controls, one study found that patients with SIH demonstrated significantly reduced CSF in the optic nerve sheath and a more straightened optic nerve angle (60). Some research has also looked at the use of transorbital ultrasound in cases of SIH. One study found that patients with SIH who had orthostatic headache had a significant decrease in optic nerve sheath diameter, as measured by ultrasound, when shifting from the supine to the upright position (61). This group was compared to patients with SIH who had no orthostatic headache and with control patients (61). As a final note about MRI, it is important to remember that about 15–20% of patients with SIH can have normal MRI of the brain (45).

MRI spine abnormalities seen in SIH include extradural fluid collections that may be focal or extend along several vertebral segments, spinal dural enhancement, meningeal diverticula and dilated nerve root sleeves, and engorgement of epidural venous plexus (12). Although it is possible, especially with highly T2-weighted images, to approximate the site of the CSF leak, the MRI of the spine does not appear to be a substitute for myelography in identifying the site of the leak for more targeted treatment approaches (62). However, both MRI brain and MRI spine are sensitive diagnostic techniques for suspected cases of SIH and are not invasive, meaning they do not involve a dural puncture, and do not involve radiation.

Box 38.3 SEEPS: a mnemonic for common magnetic resonance imaging head abnormalities seen in spontaneous intracranial hypotension (4)

S	Sagging of the brain
E	Enhancement of pachymeningeal
E	Engorgement of venous structures
P	Pituitary hyperaemia
S	Subdural fluid collections

Source data from *JAMA*, 295, Schievink WI. Spontaneous spinal cerebrospinal fluid leaks and intracranial hypotension, pp. 2286–2296, 2006.

Myelography

CT myelography (CTM) involves the intradural injection of contrast to identify the presence and location of a spinal CSF leak. Extradural fluid collections, meningeal diverticula, and extradural extravasation of contrast into the paraspinal soft tissues are common abnormalities that are seen in the setting of SIH (12). Although the extradural fluid collections can be quite focal, it is also possible that they may extend several spinal levels. With the invasive forms of myelography, about 10% of patients can have retrospinal fluid collections of contrast at the C1–2 level (45). This does not correlate with the site of a CSF leak and is felt to be a false localizing sign (45).

CTM is conventionally a static diagnostic study, not dynamic. It is important to note that the rate of a CSF leak may vary from very slow to intermittent to very fast. Thus, the results of CTM are influenced by the rate of CSF leakage, which can be a challenge at both extremes, when the CSF leak flow is very slow or very fast. In the setting of slow-flow CSF leak, delayed CT scanning or MRI myelography with intrathecal injection of gadolinium may be helpful (63). Digital subtraction myelography (DSM) (64,65) and ultrafast dynamic CTM (66,67) are techniques that have excellent temporal resolution versus a standard CTM. These techniques are useful for CSF leaks with a rapid flow rate. Although, CTM has been the gold standard for diagnosis of spinal CSF leaks, a diagnostic technique that does not involve a dural puncture or radiation, and is not influenced by the rate of CSF leak flow is needed.

MRI myelography, which involves intrathecal injection of gadolinium, can be helpful in the identification of the site of a slow CSF leak. However, intrathecal use of gadolinium is off-label and this technique should be considered only when the diagnosis of the CSF

leak is highly suspected and when the site of the CSF leak has not been detected by other diagnostic techniques such as CTM (63).

A group of researchers at the Mayo Clinic in Rochester, New York, employ spinal MRI to plan subsequent investigations (68). They use spinal MRI first and then determine if CTM is needed and, if so, what type of CTM to do (conventional vs dynamic). If the spinal MRI does not localize the leak, but extradural fluid is present, then a dynamic CTM is performed. If extradural fluid is not present, a conventional CTM is performed. This algorithm has resulted in a reduction of CTMs in general and has also minimized unnecessary dynamic CTM. This is beneficial as it results in reduced radiation exposure and fewer invasive procedures for patients, and cost savings for the healthcare system.

As previously indicated, a more recently recognized cause of CSF leaks is a CSF venous fistula. A CSF venous fistula is a direct communication between CSF in the subarachnoid space and a paraspinal vein, with usually negative findings on myelography. Kranz's group at Duke University Medical Center (Durham, NC, USA) have described a recent finding on CTM that may help aid the recognition of a CSF venous fistula as the underlying cause of the CSF leak (48). The 'hyperdense paraspinal vein' sign is a hyper-attenuated paraspinal vein that is seen in close proximity to the area of the CSF venous fistula. This is felt to occur as a result of rapid passage of myelographic contrast into the venous system via the fistula (48).

DSM involves digital subtraction X-rays acquired during intrathecal injection of contrast via lumbar puncture. This specialized technique may be useful as an adjunct to more commonly used modalities, particularly for (i) high flow or fast leaks, without precise localization of the leak; (ii) when a CSF leak occurs as a result of a CSF venous fistula; and (iii) for localizing leaks ventral to the spinal cord (45,64,65,69).

It is important to note that there are different types of CSF leaks and imaging findings can vary based on the type of leak suspected (69). Dr Schievink's group at Cedars-Sinai (Los Angeles, CA, USA) reviewed 568 patients for the type of CSF leak (at surgery) and compared this to spinal MRI or myelography findings (69). They identified four major groups of CSF leaks at the time of surgery: dural tears, meningeal diverticula, CSF venous fistulas, and an indeterminate/unknown group. They found that extradural fluid collections commonly occur with dural tears (in nearly 100% of patients), but occur in only about one-fifth of patients with meningeal diverticula, and in none of the patients with CSF venous fistulas. So, this may explain why certain patients show few or no findings on routine testing.

Based on the currently available evidence and clinical experience, an MRI of the brain with gadolinium contrast is the most sensitive and least invasive investigation to detect the presence or absence of SIH. An MRI of the spine without contrast may definitively demonstrate the presence of an extradural fluid collection and a spinal CSF leak; however, myelography is still the gold standard for CSF leak localization. Depending on the speed of the leak or extradural fluid collections, standard CTM, dynamic CTM, DSM, or MRI myelography may be pursued.

Treatment

The treatment of SIH begins with conservative measures, usually for a few days to a few weeks, depending on the severity of symptoms, to see if the CSF leak will seal itself over (11,12,70,71). In some cases, these conservative measures are sufficient and no other interventions are required.

Conservative measures for treatment include lifestyle modifications, such as bed rest, caffeine, and hydration, as well as medications (11,12). Caffeine does provide symptomatic benefit for many patients, but the effect is short-lived. Several cases using various analgesics, theophylline, and corticosteroids have been reported in the literature (72,73). Success with these medications is highly variable and inconsistent (10–12). With regard to corticosteroids, various doses and forms have been used, such as prednisone, methylprednisolone, fludrocortisone, and dexamethasone (73). It is not clear how steroids improve symptoms related to SIH. It is proposed that they work via four possible mechanisms. These include improving brain oedema and reducing inflammation, encouraging fluid retention, reducing CSF hyperabsorption, and increasing reabsorption of extradural fluid (73). However, among those who have improvement of their symptoms, the benefits are usually temporary. Given the significant side effects of steroids, long-term use is also not appropriate (11). No randomized controlled trials have been performed in SIH with any medications.

In rare cases where the patient is decompensating quickly from a neurological point of view, such as a coma, urgent volume replacement may be needed to stabilize the patient. Intravenous saline infusions, as well as intrathecal fluid injections, such as dextran, have been reported as providing limited and temporary improvement in patient symptoms (11,12). The underlying cause, i.e. the CSF leak, must, however, be managed as quickly as possible.

When conservative measures have failed after an appropriate trial, the mainstay of treatment is a large-volume epidural blood patch (EBP) (10–12). The EBP entails the injection of autologous blood into the epidural space. If the site of the CSF leak is not known, a blind or non-directed blood patch is often done in the lumbar region. When the site of the leak is known, a directed or targeted blood patch can be performed in the region of the leak (11,12).

It is not known exactly how the EBP works, but it is felt to act in two ways. Firstly, volume replacement, which is felt to lead to the immediate effects of the EBP. Secondly, sealing of the dural defect, which is likely a delayed effect of the EBP (11,12). Sealing of the leak is proposed to occur from dural tamponade. It may also restrict CSF flow, restrict CSF absorption, and potentially change dural resistance or stiffness (74).

Response to the EBP is quite variable with regard to the onset of benefit (instant to hours), degree of benefit (none to full resolution of symptoms), and duration of effect (hours to long term) (11,12). Overall, it appears that in those receiving a first non-directed EBP, about one-third have good and long-lasting response. Many patients will require a second or third EBP before any benefit is noted. With a second EBP, another 20–33% of patients experience relief and an additional 50% have benefit with subsequent EBPs (74). A minimum of 5 days between EBPs is recommended.

It is important to note that SIH is a different condition than post-dural puncture headache (PDPH). In PDPH, given a relatively clean puncture of the dura at a known site and no associated complex anatomy, the response to an EBP is excellent. About 90% of patients have full and lasting benefit from a first EBP and essentially all respond fully to a second EBP (11,12). The CSF leak(s) from SIH are complex in anatomy and location, and may be multiple, leading to

a lower success rate with EBPs (11,74). As a result, many experts advocate a high-volume EBP when possible and as tolerated by the patient. Typical EBP volumes for PDPH are in the range of 10–20 ml. In SIH, a volume of 20–50 ml is generally recommended (11,74). The patient symptoms, such as radicular pain or intense back pain, are the limiting factors for the volume injected (74).

Ferrante et al. (75) have recommended the use of acetazolamide 18 hours and 6 hours pre-EBP procedure, and have shown higher success rates in their group of patients (75). They suggest that acetazolamide may decrease CSF flow or pressure across the leak and provide a higher chance of success for the EBP. Their work remains to be reproduced by others and more studies are required to determine if acetazolamide does, indeed, help.

Some centres use fluoroscopy and contrast material while performing EBPs. This can be helpful to demonstrate the epidural location of injection, the level, and the spread. However, it does not appear to improve the chances of success (74).

Wu et al. (76) performed a retrospective analysis of 150 patient cases who had targeted EBP for SIH (76). Factors predicting response to the first EBP were (i) volume of injected blood; (ii) length of the anterior epidural CSF collection; and (iii) midbrain–pons angle. When the EBP volume was ≥ 22.5 ml response rate was 67.9% versus a response rate of 47% when the EBP volume was < 22.5 ml ($P = 0.01$). When the anterior epidural CSF collection length was < 8 segments, the response rate was 72.5% versus 37.3% when the anterior epidural CSF collection was > 8 segments (odds ratio 4.4; $P < 0.001$). Patients with anterior epidural CSF collection involving < 8 segments and an injected EBP volume of > 22.5 ml had an 80.0% response rate, while patients with anterior epidural CSF collection involving > 8 segments and a midbrain-pons angle < 40° had a 21.2% response rate (76).

Complications after EBPs are generally uncommon. Some neck and back pain for hours to a few days after the EBP may occur. This is likely as a result of blood tracking back into the subcutaneous and muscular tissues of the neck and back (74). In rare cases, a dural puncture may occur and lead to worsening of headache. Other rarer complications include persistent haematoma or abscess, delayed neurological deficits, chronic back pain, arachnoiditis, intracranial hypertension, acute meningeal irritation, and post-procedure visual changes (74). Contraindications to EBP include local infection at the proposed site of injection, sepsis, coagulopathy, and inability to cooperate (74).

There are no specific guidelines or protocols in determining how many EBPs should be done in a patient. Many authors advocate for doing up to three non-directed EBPs before proceeding to more costly tests to localize the CSF leak. Once the leak is found, directed EBPs can then be performed (74).

Studies indicate that targeted EBPs have a higher chance of success (62,77–80). A Korean study assessed the efficacy of directed EBPs versus non-directed EBPs (79). This study had several limitations and should be interpreted with caution. For example, it was not blinded or randomized, and was retrospective in design. The volume of blood injected was 9–20 ml in the non-directed EBP group, and 10–15 ml autologous blood mixed with contrast medium (1–2 ml iopamidol) under fluoroscopic guidance in the directed EBP group (79). The authors defined a good outcome as complete recovery or minimal symptoms, and a poor outcome as persistent symptoms requiring a repeat EBP (79). Thirty-one patients received a targeted EBP; 27 (87%) had a good outcome (79). The other four patients had a repeat directed EBP and went on to have a good outcome. Of 25 patients with a non-directed EBP, 13 (52%) had a good outcome (79). In this study, no EBP-related complications were reported (79). Several subsequent case series have also demonstrated higher success rates with directed blood patches (vs non-directed) and generally better results with higher-volume EBPs (vs lower-volume patches) (81).

It is important to note, however, that targeted EBPs that are done at higher levels, such as thoracic or cervical, may be associated with slightly higher complication risks, including compression of the spinal cord and nerve roots, intrathecal blood injection, and chemical meningitis (74).

In cases where the site of the CSF leak is known and repeated directed EBPs are not successful, CT-guided percutaneous fibrin glue injections can be performed (82). Fibrin glue (fibrin sealant) is a bovine product that allows the blood to coagulate by forming a stable fibrin clot that can assist haemostasis and wound healing (82). There are possible side effects, including infection or bleeding at the site, arachnoiditis, and fibrous scar formation (82). In rare cases, sensitization and anaphylaxis can occur (74,82). For this reason, 3–6 months is recommended between fibrin glue injections (74). Pretreatment with diphenhydramine may help reduce sensitization and anaphylaxis rates. Variable success rates have been reported with these injections (74,82).

Neurosurgery is reserved as the final intervention if everything else fails and the patient continues to have disabling symptoms. The site of the leak should be known before surgery is undertaken (10–12). The surgery is often intricate and complex. Sometimes the anatomy or pathology differs at the time of surgery than expected from the imaging findings (11,12,83). Various techniques can be used to repair the leak. For example, leaking meningeal diverticula can be ligated with metal aneurysm clips or the leak can be sealed with a muscle pledget. In some cases, gel foam and fibrin sealant can be used at the leak site. In other cases, the dural rent can be repaired with sutures (10,83). Most patients appear to have some improvement of symptoms after surgery, but large studies are lacking (83).

Screening patients with spontaneous intracranial hypotension for connective tissue disorders, cardiac abnormalities, and vascular pathology

SIH has been associated with connective tissue disorders. A 2013 study from Cedars-Sinai Medical Center (84) enrolled a consecutive group of 50 patients diagnosed with SIH and found that nine patients had heritable connective tissue disorders, which included Marfan syndrome, Ehlers–Danlos syndrome, and others. In seven of these patients, SIH was the first manifestation of their illness. The authors suggest that patients with SIH should be screened for connective tissue disorders and vascular abnormalities. Our recommendation would be to use a clinical questionnaire to screen patients. If there are concerns based on this, the patient can then be referred to a medical geneticist for further assessment and genetic testing if warranted.

An echocardiogram is also suggested to assess for valvular disease (e.g. mitral valve prolapse) and dilatation of the aortic root (85). In

this 2014 study, the rate of cardiovascular abnormalities detected for the same cohort of 50 patients with SIH seen at Cedars-Sinai was quite high (85). Six patients had aortic root dilatation and three had valvular heart disease ($n = 9/50$ (18%)) (85). Only two of the nine patients had an underlying connective tissue disorder, indicating that cardiovascular pathology can occur even in patients with no known connective tissue disorders.

In addition, vascular abnormalities occur with higher frequency in patients with SIH than in controls. One study showed intracranial aneurysms in 9% of patients versus 1% of controls (45). So, patients with SIH should have intracranial vascular imaging at one point during their assessment, either with CT angiogram or magnetic resonance angiogram (MRA). Those with an established connective tissue disorder, such as Marfan syndrome, should be screened further with MRA of the neck, chest, abdomen, and pelvis, because they are at risk of large arterial aneurysms (45).

Complications

Subdural haematomas can occur alone or in conjunction with subdural hygromas, which are more common (11,12). If the haematoma is large and exerting mass effect, it may need to be surgically evacuated. However, it must be kept in mind that it can reaccumulate if the underlying cause—i.e. the CSF leak—is not addressed. Therefore, the CSF leak must be treated as soon as the patient is stable (11,12).

After treatment of a CSF leak, rebound intracranial hypertension is occasionally encountered (11). Often the headache phenotype changes and patients headaches become frontal or retro-orbital in location. Other features of increased intracranial pressure, such as blurred vision, nausea, and vomiting, may occur. Many patients will have mild symptoms, but a few may have more severe symptoms. Acetazolamide, a carbonic anhydrase inhibitor that decreases production of CSF, and time may help. The patient should be monitored carefully and reassessed at regular intervals to ensure resolution over time.

Rarely, cerebral venous sinus thrombosis or bi-brachial amyotrophy are seen (11,12,86–88). Cerebral venous sinus thrombosis should be on the differential diagnosis when there is a sudden change in the headache character and/or there are new neurological symptoms or signs. Bi-brachial amyotrophy can be seen in the context of extra-arachnoid fluid collections, usually in the ventral cervical spine (11,88). In very rare cases, superficial siderosis may occur, as a remote complication of prior CSF leaks (89,90). Fluid collections are typically seen in a similar distribution as in bi-brachial amyotrophy (11). Other more recently recognized complications include frontotemporal dementia (behavioural variant), diffuse non-aneurysmal subarachnoid haemorrhage, spinal cord herniation, and brainstem infarction (91,92).

Prognosis

The majority of patients with SIH have a good prognosis, recovering fully with conservative measures or EBPs. Some require fibrin glue injections or neurosurgery, and improve with these measures. Unfortunately, a portion of patients will not respond to any treatment modality and remain symptomatic and disabled for years (11,12). It is important to ensure that there are no other headache diagnoses contributing to their symptomatology, and to ask about change in headache character during follow-up visits.

CSF leaks that have been successfully treated may recur in the future or patients can develop new sites of leak down the road (11). There is a great deal of variability in the frequency of recurrence and time after the first presentation. Large studies in this area are lacking and it is unknown what percentage of patients have recurrence. Patients should be vigilant in returning to see the physician if they have recurrence of symptoms or a new headache.

Conclusion

SIH is a disorder classically presenting with orthostatic headache and MRI findings of pachymeningeal enhancement and sagging of the brain. However, the clinical presentation and imaging findings can be broad and quite variable. The headache is not always orthostatic, there are many other neurological symptoms that can accompany the headache, and imaging can sometimes be normal. A high degree of suspicion must be exercised to diagnose the atypical forms of SIH.

Over the years, we have come a long way in the imaging modalities used to diagnose SIH and CSF leaks. Non-invasive techniques such as MRI scans of the spine are now favoured over invasive and radiation-intensive techniques such as CTMs. However, each technique has its advantages and disadvantages, and some patients will need several tests to identify the leak. Still, the leak may not be found in every case.

Treatment with an EBP is recommended when conservative measures have failed. High-volume non-targeted or blind patches can be done initially, as a certain portion of patients will respond to these. However, if there is no sustained benefit, efforts should be expended in finding the leak site and doing a targeted blood patch if possible. There is some evidence that high-volume targeted blood patches provide a higher chance of success than non-targeted blood patches. If several high-volume blood patches fail, then fibrin glue injections and neurosurgery are other options in patients with known leak sites.

Although the prognosis is generally felt to be good in patients with SIH, those presenting to headache centres are usually patients that are more severely affected and disabled. As a result, prognosis is good in some cases but not others. Patients can have disabling headaches for years, despite multiple blood patches and other interventions. Some can have success with fibrin glue and neurosurgery, but others do not have long-term benefit from these measures. In such cases, it is always important to reassess the patient and ensure that there are no other contributing factors or other possible headache diagnoses.

As further advances are made in neuroimaging and we gain further knowledge of this fascinating and complex condition, we hope that finding the site of the CSF leak will become easier and treatments will become more refined. Future studies should focus on prospective and systematic data collection from these unique patients to allow us to gain a better understanding of the natural history of this condition, to determine what imaging modalities would be best, and to determine the best course of management.

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39

Headache associated with high cerebrospinal fluid pressure

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History of idiopathic intracranial hypertension

Idiopathic intracranial hypertension (IIH) is a disorder of raised intracranial pressure (ICP), almost always associated with papilloedema, in the absence of underlying central nervous system (CNS) pathology. Although several authors had documented features of IIH in the preceding decades, it was first described in 1893 by the German physician Heinrich Quincke (1842–1922), the inventor of the lumbar puncture (LP) needle. In 1902 he published a monograph, 'Die Technik der Lumbalpunktion', in which he reported 10 cases of raised ICP where two women conformed to current criteria for IIH. Both suffered headaches and had papilloedema and raised cerebrospinal fluid (CSF) pressure, with normal CSF composition. Quincke called the syndrome 'meningitis serosa' and postulated that an increase in CSF secretion was mediated by the autonomic nervous system, with possible underlying causes of head injury, stress, excessive alcohol, pregnancy, influenza, and otitis media (1).

The term 'pseudotumor cerebri' was introduced in 1904 by Quincke's countryman, Max Nonne (1861–1959), when he reported 18 patients with raised ICP and no underlying intracranial mass lesion. Several of these patients were found to have underlying dural venous sinus thrombosis (1), and, although they did not conform precisely to the modern definition of IIH, this moniker has remained in use since then. Over the years, the syndrome has also been called hypertensive meningeal hydrops, toxic hydrocephalus, pseudo-abscess, otitic hydrocephalus, and many other terms, exposing the poor understanding of the underlying pathophysiology of the disease.

In 1937, Walter Dandy (1886—1946), an American neurosurgeon, described 22 patients with increased ICP without brain tumours. All of these patients presented with headache, and most also complained of blurred vision, dizziness, vomiting, and drowsiness. Dandy also documented many other signs and symptoms that were experienced by these patients, including buzzing in the ears, fundus abnormalities, stumbling gait, episodic numbness, and drowsiness. He summarized the findings of increased CSF opening pressure (250–500 mm CSF), normal CSF contents, and small ventricles on ventriculography (2).

Joseph Foley coined the term 'benign intracranial hypertension' in 1955 in an attempt to simplify the nomenclature and contrast the syndrome with elevated ICP secondary to brain tumours and other compressive processes (3). Although not associated with intracranial mass lesions, work by Corbett and Wall in the 1980s and 1990s demonstrated the significant loss of vision associated with IIH through the effects of severe or chronic papilloedema (4). The adjective 'benign' was subsequently dropped and replaced by 'idiopathic' to denote both the unknown aetiology of the syndrome, as well as the less-than-benign visual outcomes that can result from progressive or poorly managed disease. Advances in neuroimaging technology and recognition of additional secondary causes of intracranial hypertension further advanced the understanding of IIH. The Dandy criteria (2) were modified in 1985 by Smith, revised again in 2004 by Friedman and Jacobson (5), and updated most recently by Friedman, Liu, and Digre to incorporate our understanding of these factors and to further exclude other underlying causes of raised ICP (see **Box 39.1**) (6).

Epidemiology

IIH is considered a rare disease, with an annual incidence of around 1 in 100,000 people and an onset between 11 and 58 years of age, with an overall mean age of onset of 31 years (7). The incidence among women aged 15–44 years is 3.5 in 100,000, rising to 19 in 100,000 in obese women aged 20–44 years who are at least 20% heavier than ideal weight (4). However, most epidemiological studies were published prior to 2000, and the incidence has increased in correspondence with the rise in obesity seen in society (8). The female-to-male ratio is 4–8:1, with > 90% of patients being obese women of childbearing age (9). One study showed that men were, on average, 9 years older than their female counterparts, and there was no difference in rates of obesity based on sex (9). Men are more likely to develop vision loss than women with IIH (9,10).

IIH may occur at any age in children; however, epidemiological studies show that it is more likely to occur in older children and adolescents (12–15 years) than in younger children (2–12 years) (11–13). It is exceedingly rare in infancy. IIH appears to be a different disease

Box 39.1 Diagnostic criteria for pseudotumor cerebri syndrome

A diagnosis of pseudotumour cerebri syndrome (PTCS) is 'definite' if the patient fulfils criteria A–E. The diagnosis is considered 'probable' if criteria A–D are met, but the measured cerebrospinal fluid (CSF) pressure is lower than specified for a 'definite' diagnosis. Idiopathic intracranial hypertension is diagnosed if no secondary cause is found.

1 Required for diagnosis of PTCS:
   - **A** Papilloedema
   - **B** Normal neurological examination except for cranial nerve abnormalities
   - **C** Neuroimaging: normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion, and no abnormal meningeal enhancement on magnetic resonance imaging (MRI), with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and MR venography for others. If MRI is unavailable or contraindicated, contrast-enhanced computed tomography may be used
   - **D** Normal CSF composition
   - **E** Elevated lumbar puncture (LP) opening pressure (> 250 mm CSF in adults and > 280 mm CSF in children (250 mm CSF if the child is not sedated and not obese)) in a properly performed LP.

2 Diagnosis of PTCS without papilloedema:
   - In the absence of papilloedema, a diagnosis of PTCS can be made if B–E above are satisfied, and, in addition, the patient has a unilateral or bilateral abducens nerve palsy
   - In the absence of papilloedema or sixth nerve palsy, a diagnosis of PTCS can be 'suggested' but not made if B--E from above are satisfied, and in addition at least three of the following neuroimaging criteria are satisfied:
     (i) Empty sella
     (ii) Flattening of the posterior aspect of the globe
     (iii) Distention of the peri-optic subarachnoid space with or without a tortuous optic nerve
     (iv) Transverse venous sinus stenosis.

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process in prepubertal children than in postpubertal adolescents and adults, as evidenced by an almost equal male-to-female ratio, as well as a less definitive association with obesity (11). A study examining trends in obesity in 40 paediatric patients with IIH found that 43% of patients aged 3–11 years were obese, whereas 81% of those in the 12–14-year age group and 91% of those in the 15–17-year age group met the criteria for obesity (11). In a recent large study of paediatric IIH, three subgroups were identified: a young group that was not overweight, an early adolescent group that was either overweight or obese, and a late adolescent group that was mostly obese (14).

The cost of IIH has not been truly established, but hospitalization costs are four times more than for an average individual without IIH and estimated at $444 million dollars per year for direct and indirect costs (15).

Pathophysiology

Since the earliest accounts, obesity, female sex, menstrual irregularities, and endocrine disorders have been described as common associations of IIH; however, in order to understand the aetiology of headache in IIH, it is first important to review the mechanics of CSF flow and the theories underlying the pathophysiology of raised ICP in this disease process. ICP is a function of the volume of the contents of the cranial cavity (CSF, brain parenchyma, vasculature and its contents, dura). Any imbalance in one or more of these compartments can lead to a rise in ICP and compression of structures, as there is little room for expansion in this fixed, enclosed space. The expansion of CSF volume is of particular interest, as elevated ICP is a diagnostic criterion for the diagnosis of IIH. CSF is produced in the choroid plexus of the lateral and fourth ventricles at a rate of 0.36 ml/minute or 400–500 ml/day. After secretion into the ventricles, it flows throughout the ventricular system and enters the subarachnoid space via the foramina of Luschka and Magendie. Here the CSF bathes the cerebrum, cerebellum, and spinal cord before being absorbed through the arachnoid villi into the dural venous sinuses. There is also evidence that a portion of the CSF cycles through the brain interstitial space, enters the parenchyma along perivascular spaces that surround penetrating arteries, and is cleared along paravenous drainage pathways (16). The entire volume of CSF is 125–150 ml and is replaced every 6–8 hours. Normal CSF pressure ranges from 70 to 200 mm CSF in adults and up to 280 mm CSF in children (17,18).

The exact mechanism of the rise in CSF pressure in IIH is still unknown at this time. There is no evidence for either increased CSF production or cerebral oedema in IIH; thus, proposed theories include reduced CSF absorption and increased cerebral venous pressure. The site of impaired absorption may be at the level of the arachnoid granulations, paravenous drainage pathways, peri-olfactory lymphatics, or in the dural venous sinuses. Some other possible causes of IIH include intracranial venous hypertension and abnormal vitamin A metabolism (19).

There are a multitude of conditions and drugs that have also been associated with raised ICP; the best substantiated are listed in Box 39.2, and the reader is referred to Digre and Corbett's comprehensive

Box 39.2 Conditions and medications associated with intracranial hypertension

Medications
- Tetracycline and related antibiotics.
- Corticosteroid withdrawal.
- Vitamin A and related tretinoin compounds.
- All-trans retinoic acid.
- Lithium.
- Levonorgestrel.
- Nalidixic acid.
- Thyroid hormone replacement in children.

Medical conditions
- Obesity.
- Renal failure.
- Severe anaemia
- Turner syndrome.
- Hypoparathyroidism.
- Polycystic ovarian syndrome.
- Circulatory conditions.
- Right heart failure.
- Impaired cerebral venous drainage (i.e. jugular vein, cerebral venous sinuses).

review for a more extensive list (7). These should be adequately ruled out in order to make the diagnosis of IIH, as it is a diagnosis of exclusion. The mechanism of elevated ICP in the majority of these causes, as well as in the idiopathic form, is still poorly understood at this time. A detailed discussion of all of the theories underlying the aetiology of elevated ICP is outside of the scope of this text; however, the reader is directed to other excellent reviews of the subject (20,21).

As the brain parenchyma is insensate, how then does raised ICP lead to headache in IIH? Theoretically, it is felt to be related to compression of and traction on pain-sensitive structures within the intracranial vault. These include blood vessels (both arterial and venous), dural venous sinuses, meninges, cranial nerves, and cervical nerves. Afferent projections from these structures are transmitted via the trigeminal system and nerves C1 and C2 to the nucleus caudalis of the spinal trigeminal nucleus (STN), which runs from the level of the pons to the upper cervical spinal cord. The STN receives information regarding pain and temperature sensation from face and orofacial structures, as well as the intracranial structures mentioned earlier. Ascending fibres from the STN then decussate as they travel up through the brainstem as the trigeminal lemniscus or the ventral trigeminothalamic tract to terminate in the ventral posteromedial nucleus of the thalamus. This nucleus then sends the signals to higher cortical structures where pain sensation is brought to consciousness (22). The distribution of afferents to the trigeminal nucleus caudalis helps to explain the often holocranial distribution of IIH-related pain, as well as referred pain to the eyes and cervical regions.

Despite our understanding of the complex innervation of the head and intracranial cavity, the exact mechanism underlying IIH-related headache pain is still unknown. A definitive causal relationship between ICP and headaches has not been made, as low ICP can also result in headache (both are likely due to mechanical deformation of the meninges). Fay and Kunkle, in 1925 and 1942, respectively, artificially elevated ICP in patients, as high as 680 mm CSF in Kunkle's investigation (23,24). Some of Fay's patients reported frontal and temporal headaches; however, many had no headaches (23), and neither of Kunkle's patients experienced headaches in the setting of artificially elevated ICP (24). In 1974, Johnston and Paterson performed ICP monitoring in 20 patients with idiopathic elevated ICP using intraventricular catheters. Patients reported pain without pressure spikes and no pain with significantly elevated ICP. Some patients also continued to experience headache after normalization of ICP, documented by repeat LP, indicating that there is not a 1:1 correlation between ICP and headache (25). Headache in IIH therefore appears to be multifactorial, with elevated ICP being one factor that can trigger pain. The ongoing IIHTT (Idiopathic Intracranial Hypertension Treatment Trial) will hopefully be able to shed some light on the relationship between ICP and headache and possible therapies to help treat this potentially debilitating symptom (26).

Presentation

Symptoms

Overall, the most common presenting symptom of IIH is headache, occurring as the initial manifestation in 70–80% of adults and children and ultimately affecting > 90% of patients (26–29). The headache phenotype of IIH is not specific. It is often described as daily, bilateral, frontal, or retro-ocular; hence, IIH is in the differential diagnosis of new daily persistent headache (see also Chapter 30) (28,30). However, it may also occur intermittently and is sometimes hemicranial. It is usually moderate to severe in intensity, and some patients describe increased severity upon awakening. The headache may also be throbbing, with nausea, vomiting, and photophobia, resembling migraine (31). In one study, headache as a presenting symptom was less common in men (55%) than in women (75%) (9). There is no correlation between the presence or severity of headaches, and the LP opening pressure or papilloedema grade (28). Young children may not present with headache, either due to inability to articulate their symptoms or from lack of head pain. Neck and upper back pain are often prominent features, and cervical or radicular pain may occur (28,31).

Transient obscurations of vision (TOV) are the second most common symptom, occurring in 50–70% of patients (26,31). TOV are described as dimming, greying-out, or complete vision loss in one or both eyes, usually lasting seconds to a minute. Vision returns to baseline between episodes. They may be provoked by eye movements (particularly upward gaze) and changes in posture, as in arising from a seated or stooped position. They indicate the presence of papilloedema and likely arise as a result of transient ischaemia to the optic nerve. TOV may also occur with optic disc drusen but are rarely reported in patients with papilloedema from other causes. They do not predict vision outcome in IIH.

Pulsatile tinnitus is present in about half of patients and is likely under-reported by patients unless specifically inquired for. Patients report hearing their own heartbeat or a whooshing noise in their ears or head, which may sometimes be loud enough to prevent sleep. Other, less common non-visual symptoms include muffled or decreased hearing, neck stiffness, arthralgias, ataxia, and low back pain (31).

Visual symptoms range from non-specific blurred vision to severe vision loss and often reflect the pattern of visual field abnormality. Patients may see their physiological blind spot, which is normally not noticeable. Descriptions of this symptom are a dark spot to the side with temporal blind spot enlargement or as difficulty seeing words or parts of words on the printed page with nasal enlargement of the blind spot. Others report dim or dark vision or loss of peripheral ('tunnel') vision. Central vision loss early in the course, with impaired ability to see, read, or distinguish colours, is generally a bad prognostic sign.

Diplopia is present in one-third to two-thirds of patients and is generally binocular, resolving when either eye is occluded (28,31). It is usually horizontal and worse at distance than at near. Monocular diplopia may occur if macular oedema is present.

Signs

The most important findings are related to the neuro-ophthalmic examination, particularly visual acuity, perimetry, ocular motility, and the fundus examination. The visual acuity, measured with best correction, is most often normal. Decreased central acuity at the time of presentation indicates either macular oedema or optic nerve compromise and often portends a poor prognosis. Optic neuropathy occurs from direct compression of the nerve from elevated CSF pressure in the peri-optic subarachnoid space or ischaemic optic

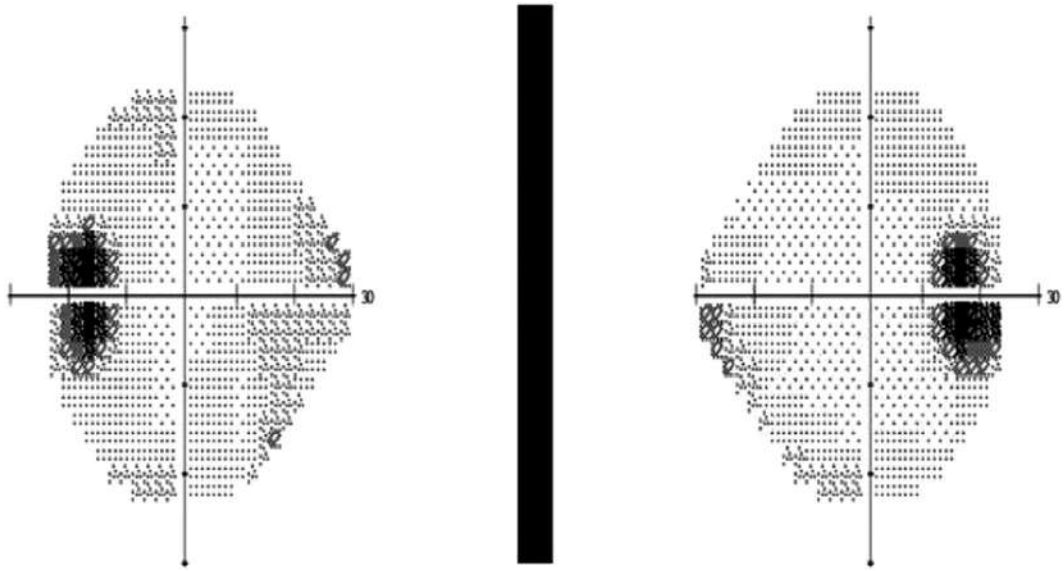

Figure 39.1 Humphrey visual fields demonstrate bilateral enlarged blind spots and early nasal depression bilaterally.

neuropathy. Vision loss from the former cause is often reversible in the early stages with treatment, while vision loss from ischaemia is permanent.

Evaluation of the visual field is of paramount importance, as most visual morbidity of IIH is a consequence of visual field loss. Automated or kinetic perimetry is necessary for adequate assessment. Confrontation visual fields are not sensitive enough to detect most visual field abnormalities in IIH; thus, a defect detected using confrontation testing is generally serious. Enlargement of the physiological blind spot is the most common and earliest sign, representing the oedematous and expanded optic nerve head. Visual field loss in IIH arises from impairment of the retinal nerve fibre layer, producing characteristic arcuate defects, nasal step, and peripheral constriction of the field (see Figure 39.1). Perimetric assessment is utilized throughout the course of the disease to monitor the patient's progress.

Unilateral or bilateral abducens nerve palsies are the most frequent ocular motility abnormalities in adults and children, a non-localizing indication of increased ICP producing an esotropia on examination. Other ocular motor nerve involvement (III, IV) is less common, and generalized ophthalmoparesis rarely occurs (32). Abnormalities of cranial nerves III, IV, VII, IX, and XII have been documented and usually resolve with adequate treatment of elevated ICP (33,34).

The hallmark of IIH is papilloedema, which is required in the acute phase for diagnosis. The timing of the onset of papilloedema likely varies among patients and is occasionally not present if the clinical evaluation occurs very early. Previous optic atrophy also precludes the development of papilloedema, a major consideration when evaluating the patient for recurrence, and it may be challenging to discern papilloedema if optic disc drusen are present. Early papilloedema is difficult to detect using a direct ophthalmoscope, and other methods, such as biomicroscopy, indirect ophthalmoscopy, orbital ultrasound, and fluorescein angiography, are useful techniques in such cases. Documentation of the optic nerve appearance using fundus photography is invaluable for both diagnosis and subsequent follow-up.

The Frisén system is used to grade papilloedema. Early (grade 1) papilloedema is characterized by disruption of the normal radial nerve fibre layer arrangement with greyish opacity accentuating the nerve fibre bundles. A subtle grey peripapillary halo is apparent with the indirect ophthalmoscope. There may be concentric or retinochoroidal folds. With progression of papilloedema grade, the borders of the optic disc become indistinct, with elevation of the disc margins (grade 2). The nerve head diameter increases, and the oedematous nerve fibre layer obscures one or more segments of major blood vessels leaving the disc (grade 3) (see Figure 39.2). With severe papilloedema (grades 4 and 5), the optic nerve protrudes, the peripapillary halo becomes more demarcated, and the optic cup is obliterated (35). Hyperaemia, vessel tortuosity, haemorrhages, exudates, nerve fibre layer infarcts (cotton wool spots), and optic nerve pallor are often observed but are too variable to use for staging purposes. Papilloedema will not develop in the setting of optic atrophy, which is an important consideration when considering recurrence.

Spontaneous venous pulsations are often relied upon to diagnose early papilloedema. They are best observed at the optic nerve head using direct ophthalmoscopy. Loss of spontaneous venous pulsations occurs when the CSF pressure is approximately 190 mm CSF (36). Spontaneous venous pulsations are only present in about 75% of normal individuals. Their absence does not confirm intracranial hypertension, but their presence is reassuring.

Laboratory testing

The diagnosis of IIH is predicated on the exclusion of other CNS disorders producing intracranial hypertension, such as a mass lesion, infection, malignancy, or inflammation. Magnetic resonance imaging (MRI) is the recommended imaging study for diagnosis. The brain parenchyma and ventricular size should be normal for age (37). Subtle signs of increased ICP include an empty sella, cerebellar tonsillar descent, expansion of the optic nerve sheath complex, flattening of the posterior sclerae, tortuosity of the optic nerve, and protrusion of the optic nerve papilla into the vitreous (38–40) (see Figure 39.3). If an MRI is unavailable, contrast-enhanced computed

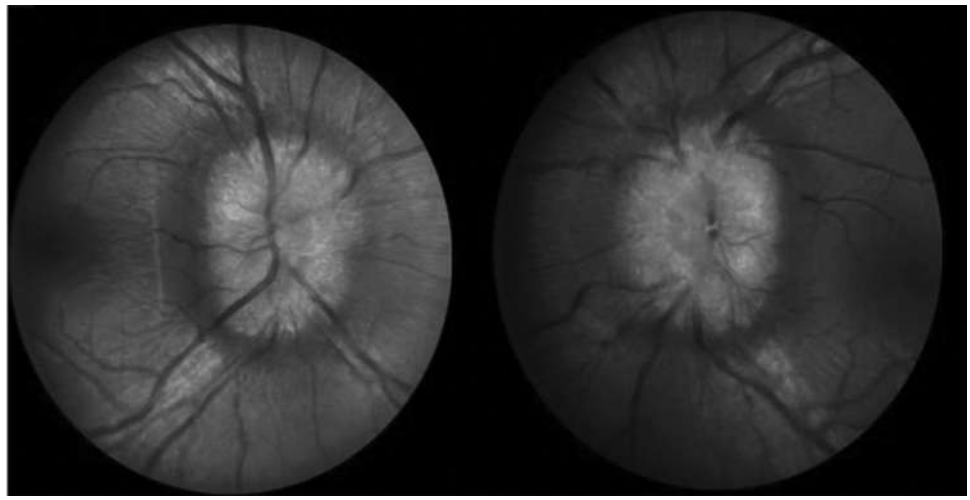

Figure 39.2 Stage 3 papilloedema with 360-degree blurring of the disc margin and obscuration of vessels as they leave the disc.

tomography may be used to exclude a brain tumour or hydrocephalus, but it will not visualize the more nuanced findings mentioned. Magnetic resonance venography may show transverse sinus stenosis (see Figure 39.4) and is recommended in atypical patients (e.g. men, children, individuals > 45 years of age) and in patients at risk (e.g. known thrombophilia, oral contraceptive use), or in those not responding to therapy to assess for a venous sinus thrombosis. The presence of transverse sinus stenosis does not correlate with disease severity in IIH (41).

A LP is required for diagnosis. The diagnostic opening pressure in a properly performed LP (patient in the lateral decubitus position, not anaesthetized) is at least 250 mm CSF in adults and 280 mm CSF in children (17). There are many factors affecting CSF pressure, which fluctuates over a wide range during the course of a day and is influenced by activity and Valsalva manoeuvres (42). The LP represents a 'snapshot in time' and should be repeated if there is any question about an erroneously high or low pressure measurement in the appropriate clinical context. CSF analysis at the time of diagnosis includes determination of glucose, protein, cell count with differential, microbiology studies, and cytology.

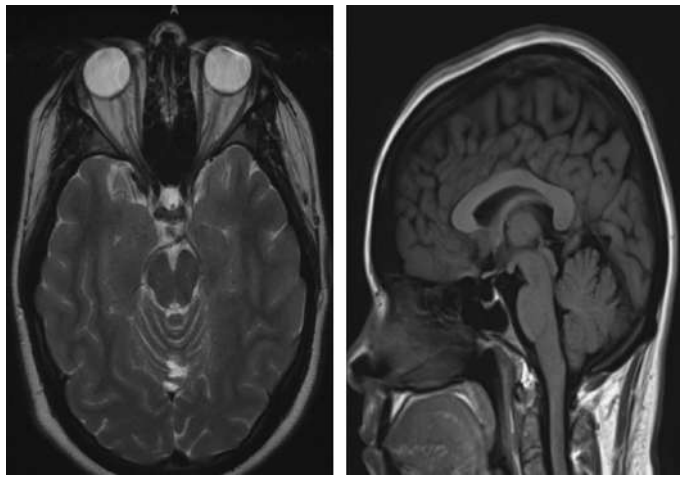

Figure 39.3 Signs of increased intracranial pressure include an empty sella, expansion of the optic nerve sheath complex, flattening of the posterior sclerae, tortuosity of the optic nerve, and protrusion of the optic nerve papilla into the vitreous.

Comorbid conditions

The most common comorbidity in adults is obesity. Menstrual irregularities reported in the older literature are likely related to obesity, rather than IIH. As the co-occurrence of sleep apnoea and intracranial hypertension in men is so frequent, sleep studies are recommended in all men and in women with symptoms suggestive of obstructive sleep apnoea to rule out this treatable cause (43–45). Anxiety and depression occur more commonly in women with IIH, who have poorer quality-of-life assessment scores than age-, sex-, and weight-matched control subjects (46). No studies to date have confirmed an association between migraine or any other primary headache disorders and the subsequent development of IIH. IIH may begin or recur during pregnancy but with no increased frequency compared to non-pregnant women in a similar age cohort (47). The incidence of polycystic ovarian syndrome has been found to be higher in IIH (48), and, similarly, metabolic syndrome may be a risk factor for development of IIH given its association with obesity. Orthostatic oedema, characterized by dependent oedema in

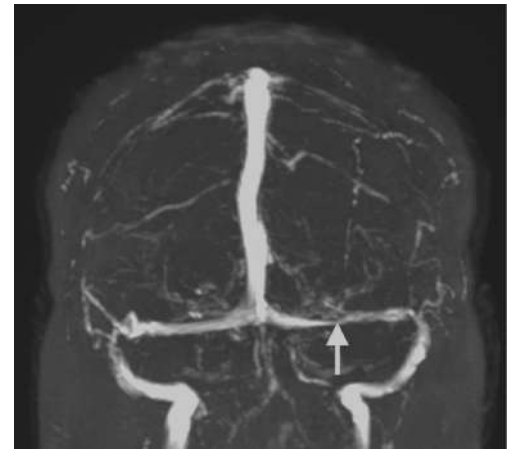

Figure 39.4 Magnetic resonance venogram demonstrating partial narrowing of the left transverse sinus.

the absence of cardiac or renal abnormalities, is associated with IIH in women (49).

Treatment

The goal of treatment in IIH is to effectively reduce ICP to minimize the effects of the major morbidities associated with the disease: vision loss from chronic or severe papilloedema and headache. It can also help to alleviate symptoms from cranial nerve palsies. There are reports of cerebral venous sinus thrombosis and subarachnoid haemorrhage occurring as a result of chronically elevated ICP in IIH (50). Secondary causes of intracranial hypertension should be treated if discovered. This includes anticoagulation for venous sinus thrombosis, discontinuation of medications associated with intracranial hypertension, treatment of metabolic and haematological disorders, and treatment of dysparathyroid and dysthyroid states. However, treating the secondary cause may not be adequate to prevent vision loss, and other medical and surgical therapies used to treat IIH are frequently necessary. Immediate management is primarily based on the duration of symptoms, evaluation of visual function, and patient characteristics. In 2015, a Cochrane Database review concluded that two randomized controlled trials showed modest benefits for acetazolamide for some outcomes but with insufficient evidence to recommend or reject the efficacy of this intervention for treating people with IIH, which was also true for any other treatments currently available (51). Since then, several results of the large IIHTT have been published (52). The commonly used medical and surgical treatment options available are discussed in the following sections. Although the IIHTT did not involve paediatric patients, treatment strategies are similar in children and adults.

Medical management

Weight loss

While the exact causal mechanism remains unknown, the relationship between weight gain, obesity, and the development of IIH is well established clinically and in the literature (12). Even non-obese patients with a body mass index < 30 are at greater risk for developing IIH if they experience a recent moderate weight gain of as little as 5–15% of their body weight. It has also been documented that loss of as little as 5–10% of total body weight can reduce symptoms of headache ,as well as ICP and papilloedema, and their attendant risk of vision loss (53,54). Subsequent weight gain is associated with recurrence of symptoms and papilloedema (12,20).

Weight loss through reduction of calorie, fluid, and sodium intake has been shown to be effective in treating IIH. In 1974, Newborg reported remission of papilloedema in all nine patients placed on a low-calorie adaptation of the Kempner rice diet of 400–1000 calories per day. Fluids and sodium intake were also restricted (55). While this is a somewhat restrictive diet, it does support the concept that weight loss is an effective treatment for IIH. Reduction in dietary intake of tyramine has also been shown to improve headache associated with IIH (56). This concept was reinforced by the findings of the IIHTT in which patients randomized to medical treatment plus weight loss and weight loss alone saw improvements in papilloedema grade and quality of life (52). More detailed findings of the IIHTT are summarized in the next section. In general, patients without vision loss (visual field defects and preserved acuity) that have grade 1 or 2 papilloedema may be managed with diet alone. They should be followed closely, and if their acuity or fields worsen, acetazolamide should be added. Weight loss alone is not an effective short-term therapy and must be combined with medical therapy in the initial management of the disease when vision loss is present (52). Weight loss and prevention of fluctuations in weight for the long-term management of obese patients with IIH cannot be understated.

Diuretics

Acetazolamide is an oral carbonic anhydrase inhibitor (CAI), which has been the mainstay of treatment of IIH for decades. It decreases CSF flow once 99.5% of choroid plexus carbonic anhydrase is inhibited, which may require up to 4 g daily (8,52). It may also promote weight loss through an anorexic effect by changing the taste of foods. Patients nearly always experience paraesthesias in the fingers, toes, and peri-oral region and less commonly have malaise. Renal stones occur in a small percentage of patients. Metabolic acidosis, indicated by lowered serum bicarbonate, indicates adherence to treatment and rarely requires treatment. A rare, but serious, idiosyncratic side effect is aplastic anaemia, which occurs in 1 in 15,000 patient-years of treatment (8). The sulfa moiety in acetazolamide differs from sulfa antibiotics, and little evidence exists to support a self-reported sulfa allergy will produce a life-threatening cross-reaction with the drug (57). Acetazolamide is generally started at 1 g daily in divided doses and increased to a maximum tolerated dose of 4 g daily as needed. Typically, 1–2 g per day is well tolerated and is sufficient to adequately lower ICP and reduce signs and symptoms.

The IIHTT was a multicentre randomized, double-masked, placebo-controlled trial investigating the effect of acetazolamide at reducing or reversing visual field loss after 6 months of treatment when added to a supervised, low sodium weight reduction programme versus the programme plus placebo. The primary outcome variable was the change in perimetric mean deviation (PMD) from baseline to month 6 in the most affected eye, as measured by Humphrey visual fields (Carl Zeiss Meditec, Dublin, CA, USA). PMD is a measure of global visual field loss, as a mean deviation from age-corrected normal values, with a range of 2 to –32 dB. Secondary outcome variables included changes in papilloedema grade, quality of life (Visual Function Questionnaire 25 and 36-Item Short Form Health Survey), headache disability, and weight at month 6. The study showed that in patients with mild visual loss (a PMD of –2 to –7 dB), acetazolamide plus diet had better visual outcomes than those taking placebo plus diet. Patients taking acetazolamide also had significantly improved papilloedema and visual quality-of-life measures, although no significant difference was found in visual acuity in the study or fellow eye. There was also no statistically significant difference between the groups with respect to headache or headache disability. The benefits of acetazolamide and diet were independent, and patients tolerated up to 4 g acetazolamide per day (52).

Seven participants (six on diet plus placebo) met criteria for treatment failure. Male patients, those with high-grade papilloedema, and those with decreased visual acuity at baseline were more likely to experience treatment failure. All but one of these patients was treated with diet alone (52). To assess the effect on papilloedema retinal nerve fibre layer (RNFL) thickness, total retinal thickness (TRT), optic nerve volume, and retinal ganglion cell layer, measurements

were derived using spectral-domain optical coherence tomography (OCT). Acetazolamide and weight loss effectively improved RNFL thickness, TRT, and optic nerve volume swelling measurements resulting from papilloedema. In contrast to the strong correlation at baseline, OCT measures at 6 months showed only moderate correlations with Frisén papilloedema grade (58).

Topiramate

Topiramate is a sulfamate-substituted derivative of fructose. It was first developed as an antiepileptic drug (AED). It is effective in treating refractory chronic partial seizures and has been used as monotherapy in adolescents and adults. It is a polypharmic AED with effects on carbonic anhydrase activity, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and γ-aminobutyric acid (GABA) receptors, as well as Ca^{2+} and Na^{+} channels (59). The use of topiramate in IIH was first reported in a prospective open-label study using both topiramate (daily dose range 100–150 mg) and acetazolamide daily (dose range 1000–1500 mg). No placebo group was included. A statistically significant improvement in visual field was found with both drugs, and no statistically significant difference was found when compared with each other. Weight loss was prominent in the topiramate group (48). The side effect profile is similar to acetazolamide; however, adverse cognitive effects can occur, and the drug is not recommended for use in patients with a history of severe depression. As a frontline drug in the treatment of migraines, topiramate is often used as a substitute or adjunct for acetazolamide in patients with IIH with predominantly migraine-like headache symptoms (48).

The loop diuretic furosemide has also been used to lower ICP in IIH. It appears to work by diuresis and reducing sodium transport into the brain. Treatment is initiated a dosage of 20 mg by mouth twice daily and gradually increased, if necessary, to a maximum of 40 mg by mouth three times daily. Potassium supplementation is given as needed. Other diuretics used in the treatment of IIH include methazolamide (in patients with renal disease), another CAI, as well as spironolactone for patients who are allergic to CAIs and thiazide diuretics.

Headache treatment

Headache associated with IIH can be debilitating and significantly affect quality of life, mood, and psychosocial status. As headache does not correlate with CSF pressure, it is often necessary to treat the headache separately in these patients. Treatment of headache should proceed with prophylactic and symptomatic therapies as tolerated with medications found to be efficacious in individual patients. Topiramate is often effective with the additional potential benefits of weight loss and mild carbonic anhydrase inhibition. Tricyclic antidepressants, such as amitriptyline and nortripyline, are useful and often not associated with weight gain at low doses. Other preventative medications associated with weight gain, such as divalproex sodium and cyproheptadine, should not be used. Corticosteroids are not recommended because of their numerous undesirable side effects (including weight gain and fluid retention) and potential rebound intracranial hypertension as they are withdrawn. For symptomatic headache treatment, acetaminophen, paracetamol, and non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, should be limited to no more than 3 days per week, to prevent the development of medication overuse headaches. Naproxen is less likely to cause medication overuse headache, and indomethacin may lower CSF pressure. Triptans may be employed if the headache phenotype is similar to migraine. Headaches may persist even after the ICP is controlled (60). We have successfully employed onabotulinum toxin A treatment in patients with persisting headaches having characteristics of chronic migraine. Mathew et al. (61) found that a combination of a diuretic and migraine preventative appeared to be the best treatment for headache associated with IIH.

Drugs used in treatment of headache in IIH are summarized in **Table 39.1**.

Therapeutic lumbar puncture

LP can be both a diagnostic and therapeutic procedure in the management of IIH. LP may relieve headache, diplopia, and papilloedema, and can reverse and/or prevent vision loss, especially in acute fulminant cases. It is not uncommon to see a lasting clinical remission following a single LP in some patients with IIH that obviates the need for further medical or surgical treatment. Some patients may also benefit from a transient lumbar drain while awaiting a more definite surgical procedure, especially in acute fulminant cases. While some patients may be managed with episodic LPs to remain asymptomatic, routine LPs for long-term management are generally not advocated as the procedure is technically difficult in obese patients, and there is a rare risk of infection associated with the procedure. The vast majority of patients will also require medical therapy and weight loss in the long-term to manage their disease. Therapeutic LPs are useful for intermittent exacerbations of symptoms and for management of IIH during pregnancy. There is no evidence to support the effectiveness of a 'large volume' LP (i.e. removal of ≥ 20 ml CSF), and post-LP headache may occur. We recommend removing enough CSF to achieve a closing pressure within the normal range (approximately 150–170 mm CSF).

Surgical management

Surgical management of IIH is indicated for patients with progressive vision loss despite maximal medical therapy and severe vision loss in the case of fulminant IIH. Surgery is not recommended as a primary treatment of headaches. The most commonly employed surgical options include optic nerve sheath fenestration (ONSF) and various CSF diversion procedures. The decision to use one or the other is often based on local preferences and the availability of surgeons versed in either procedure; some centres always perform ONSF as a first-line treatment, while some use both procedures based on the patient's symptoms and signs (e.g. ONSF for vision loss and shunt for vision loss and headaches). There are no randomized clinical trials comparing the two procedures, and outcomes are greatly dependent upon the experience of the surgeons performing the procedures.

Recently, endovascular venous stenting of the dural venous sinuses has been shown to reduce cerebral venous pressure, reduce ICP, and improve symptoms and signs in selected patients with IIH (20,62). It is still unclear, however, if primary treatment of the observed stenosis benefits patients with IIH, as it is still not certain whether stenosis is the cause or the result of raised ICP. Given the known complications of the procedure (stent migration, venous sinus perforation, re-stenosis, in-stent thrombosis, cerebral haemorrhage,

Table 39.1 Treatment of headache in idiopathic intracranial hypertension: the best treatment for the headache is usually a diuretic and a headache preventative.

Medication types	Examples	Other uses	Side effects	FDA pregnancy category
Diuretics	Acetazolamide 250–4000 mg Methazolamide 25–50 mg Furosemide 2–80 mg Chlorthalidone 100 mg	Carbonic anhydrase inhibitor; loop diuretic	Kidney stones; rash; dehydration	C CC B
Beta blockers 30 mg daily	Propranolol 20–120 mg daily Nadolol 10–80 mg daily Timolol 10–30 mg daily	Blood pressure; migraine prevention; tremor	Hypotension; reduced heart rate	C
Calcium channel blockers	Verapamil 80–240 mg daily Amlodipine 2.5–10 mg daily	Blood pressure; migraine; circulation	Hypotension; constipation; fatigue	C
Seizure medications	Topiramate 25–200 mg daily	Migraine and cluster headache	Kidney stones; anaemia; acute-angle closure glaucoma; rash	D
	Valproate 250–2000 mg/day	Migraine	Weight gain; nausea; tremor	D
	Gabapentin 100–1000 mg/day	Face pain; fibromyalgia; seizure	Drowsiness; water retention; weight gain	C
Tricyclic antidepressants	Amitriptyline 10–150 mg at night Nortriptyline 10–100 mg at night Imipramine 10–100 mg at night Desipramine 10–100 mg at night	Migraine; depression; insomnia; nerve pain	Constipation; drowsiness; dry mouth; weight gain	C
Antidepressants: SSRIs	Fluoxetine 10–60 mg daily Sertraline 25–200 mg daily Paroxetine 10–40 mg daily Citalopram 10–40 mg daily	Depression; anxiety; post-traumatic stress disorder	Dry mouth; diarrhoea; sexual side effects	C
Others				
Botulinum toxin		Chronic migraine		C

FDA, US Food and Drug Administration; SSRI, selective serotonin reuptake inhibitor.

death) and the paucity of data on the safety and long-term outcomes of venous stenting, its use at this time should be limited to selected refractory patients who cannot undergo or have failed more conventional surgical treatment.

Gastric bypass surgery has been used with some success in patients with IIH; however, is it is felt that this procedure should be reserved for morbidly obese patients who have failed other weight-loss approaches, as well as medical treatment of their IIH (63).

ONSF

ONSF is performed in cases of fulminant IIH where patients are rapidly losing vision from significantly elevated ICP or in cases of progressive vision loss in patients who are not responding to medical therapy or are non-adherent with therapy. There are a number of surgical approaches to fenestrating the optic nerves; however, the final goal is to create a window or a series of slits in the optic nerve sheath just behind the globe to release CSF under pressure causing compression of the nerve. There is large amount of literature supporting the efficacy of the procedure in protecting or improving vision in both the fenestrated and non-fenestrated eye. The mechanism of action is felt to be due to both decompression of the peri-optic subarachnoid space, as well as scarring of the surgical site, preventing further accumulation of CSF. Although not employed solely for the treatment of headaches, ONSF may reduce headache in over half of patients with IIH undergoing the procedure (64–66). The mechanism for the improvement of headaches after ONSF is unclear.

Although generally safe when performed by an experienced surgeon, ONSF is not without complications, including progressive vision loss, permanent vision loss, postoperative nerve sheath haemorrhage, and diplopia that is generally transient (67–69). Long-term failure may occur after ONSF and may require CSF diversion surgery. Overall, ONSF is felt to be a good and safe option for many patients with predominant symptoms of vision loss in IIH, especially in acute fulminant cases.

CSF diversion procedures

CSF diversion procedures include lumboperitoneal (LPS), ventriculoatrial, ventriculojugular, and ventriculoperitoneal

shunts (VPS). LPS is more commonly performed than VPS because insertion and maintenance of patency may be more difficult in the latter procedure. However, the failure rate of LPS exceeds that of VPS, and more neurosurgeons are employing VPS for the treatment of IIH. The immediate efficacy treating vision loss is well-documented (70–72). Although shunting usually reduces headache in IIH immediately after the procedure is performed, at least 50% of patients have recurrent headaches within 3 years, and most patients require a shunt revision within the first year (72). Sinclair et al. (73) reported an overall improvement in visual symptoms after shunting, but headaches remained in a majority of patients (79%) (73). Shunting is also not without complications. More than half (56%) of patients in the series of Eggenberger et al. (71) required shunt revision, and 10 of 25 patients in the series of Abubaker et al. (70) also required revisions. Other documented complications were radicular pain, abdominal pain, low-pressure headaches, and shunt infection (70–72). In-hospital mortality for new shunts is 0.5%, with 0.9% for ventricular shunts and 0.2% for lumbar shunts (74). Major causes of shunt failure include catheter or valve obstruction, low ICP, catheter migration, and lumbar radiculopathy. Over-shunting with LPS can lead to an acquired Chiari malformation or chronic intracranial hypotension. Most patients experience a postural headache, but there may be symptoms that are similar to those of elevated ICP, such as neck pain, vomiting, photosensitivity, blurred vision, transient visual obscurations, peripheral visual field loss, and sixth nerve paresis (75). Headache is less frequent in VPS than in LPS, and a programmable shunt valve with VPS can often prevent low-pressure headaches, obviating the need for re-operation (5).

Despite the apparent high rate of complications, and failure, CSF shunting procedures remain the most widely performed surgical treatment for IIH (74). They can be very useful acutely to prevent or treat devastating vision loss in selected patients.

Treatment of idiopathic intracranial hypertension in special populations: pregnancy

As IIH occurs in young women of childbearing years, IIH will be seen in pregnant women. Diagnosis, evaluation, and treatment should follow the same general guidelines as in non-pregnant women, with a few caveats. While weight loss is often promoted in non-pregnant women, women who are obese should be counselled to limit weight gain in pregnancy (47). Acetazolamide has been studied in pregnant women, and teratogenicity in their children was not greater than expected in the general population. Therefore, acetazolamide should be used when indicated in pregnant women (76).

While surgical procedures are often avoided in pregnancy, when vision loss occurs, surgery may be required. No guidelines exist for surgical treatment of IIH in pregnancy. Shunting into the abdomen of a pregnant woman is technically challenging but possible, and ONSF may be the preferred procedure (77). Delivery for women should be based on obstetric indications. If there is concern for vision loss during the second stage of labour (pushing or Valsalva manoeuvre), low-outlet forceps may be indicated. Caesarean section or operative delivery is not indicated for IIH alone and should be based on obstetric indications. Treatment of the headache in pregnancy is difficult, as medication exposures are limited. In early pregnancy, NSAIDs can be used safely (Food and Drug Administration category B in early pregnancy); later in pregnancy, because of problems of premature ductus arteriosus closure and decreases in amniotic fluid production, NSAIDs are avoided. Medications that are used to treat other headaches in pregnancy include tricyclic antidepressants and, when comorbid depression is present, serotonin reuptake inhibitors. In general, anticonvulsants (e.g. topiramate, sodium valproate) are not recommended in early pregnancy because of the risks of fetal malformations.

Prognosis

Medical treatment of IIH is seldom lifelong, and ICP-lowering agents are generally tapered and discontinued when the patient's vision status and optic nerve appearance have stabilized or when the disease has been in remission for at least 6 months (7). Clinical experience, however, indicates that it is common for patients to have headaches or chronic papilloedema while being otherwise asymptomatic with stable visual function. They may also continue to have symptoms that require medical agents to lower ICP. This suggests that intracranial hypertension, symptomatic or not, persists in many patients with IIH. In a series by Corbett et al. (78), 10 of 12 (83%) patients in long-term follow-up who underwent repeated LPs showed persistently elevated ICPs, ranging from 220 to 550 mm CSF. Recurrent symptoms and papilloedema have been reported in 8–37% of patients, often years after the initial diagnosis (7). Recurrence of symptoms may warrant reinstitution of medications, but headaches can typically be managed without diuretics or CAIs, unless there is evidence of elevated ICP documented by LP or recurrence of papilloedema.

Poor visual prognosis seems to be associated with severe acuity loss at presentation, and secondary causes such as anaemia, renal failure, and venous sinus thrombosis.

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40

Headache associated with systemic infection, intoxication, or metabolic derangement

Ana Marissa Lagman-Bartolome and Jonathan P. Gladstone

Headaches attributed to exposure to a substance

Headache attributed to exposure to a substance (previously referred to as 'toxic headaches') is a secondary type of headache disorder that occurs for the first time in close temporal relation to exposure to or withdrawal from a substance. Over the years, many substances known to induce headaches in susceptible individuals have been identified, including alcohol, prescription and illicit drugs, chemical products, food additives, and others (1–4).

It is important to recognize that it is not uncommon for primary headache disorders to be precipitated or exacerbated by exposure to certain substances. For example, cluster headache patients are often very susceptible to alcohol, and migraineurs can be particularly hypersensitive or susceptible to a wide range of exposures. It is therefore crucial when evaluating patients with headaches related to substance exposures to distinguish whether the headaches are primary or secondary. According to the third edition of the International Classification of Headache Disorders (ICHD-3), when a pre-existing headache disorder occurs in temporal relation to substance exposure, both the initial headache diagnosis and a diagnosis of 'headache attributed to a substance' should be given. The factors in favour of secondary causation or toxic headaches include close temporal association, marked worsening of pre-existing headache, evidence that the substance can aggravate the primary headache, and improvement or resolution of headache on discontinuation of the substance (5). This chapter will highlight the primary recognized headaches attributed to intoxication (see **Box 40.1**).

Toxic headaches can be subdivided into three subgroups: (i) headaches that are caused by an unwanted effect of a toxic substance (a substance that is considered toxic); (ii) headaches that happen as an unwanted effect of a normal exposure; (iii) headaches that occur as an unwanted effect of an exposure to an experimental substance (e.g. phase I-phase III studies of new medications) (6).

Headache as a side effect has been recorded with most drugs, usually merely reflecting the high prevalence of headache in the general population (rather than a specific medication-related side effect). Only when headache occurs more often after an active drug than after placebo in double-blind controlled trials can headache truly be regarded as a legitimate side effect. There is a minimum dose of exposure that is required wherein the headache follows at least half of the exposures (and at least three times), and the headache resolves when the substance is eliminated. These headaches can be induced with onset immediately or within hours after acute and occasionally with chronic exposures, which may reflect the chemical sensitivity of the headache-prone brain. The characteristics of headaches due to intoxication are generally non-specific. The headaches are often generalized, persistent, and at times throbbing, and increase in intensity with increased dosage of substances. **Box 40.2** describes the diagnostic criteria for headache attributed to substance use using the ICHD-3 (5).

Epidemiology

Published literature regarding the relative incidence of headache related to different drugs is lacking. There are also no population-based prospective epidemiological data on the incidence of substance-induced headaches (1). In 1989, Askmark et al. (7) carried out a survey of 10,506 reports of drug-induced headaches from 1972 to 1989 from the World Health Organization Collaborating Centre for International Drug Monitoring of five countries, including the USA, Australia, New Zealand, Sweden, and the UK. Of the headaches reported from these five countries and the other 27 member countries during this period, the most common headache type was migraine followed by headaches associated with intracranial hypertension and then headaches that were unclassifiable (7). Substance-induced headaches were found to be more common in older patients, especially with psychoactive drugs (8). Migraineurs, tension-type and cluster headache patients were found to have greater risk for drug-induced headache (5,9).

The common drugs that are implicated in producing headaches include non-steroidal anti-inflammatory drugs (NSAIDs: indomethacin, diclofenac), calcium channel blockers (nifedipine), histamine receptor blockers (cimetidine, ranitidine), steroids (beclomethasone,

Box 40.1 ICHD-3 categorization of headaches attributed to a substance

8.1 Headache attributed to use of or exposure to a substance
- 8.1.1 Nitric oxide (NO) donor-induced headache:
  - 8.1.1.1 Immediate NO donor-induced headache
  - 8.1.1.2 Delayed NO donor-induced headache.
- 8.1.2 Phosphodiesterase inhibitor-induced headache.
- 8.1.3 Carbon monoxide-induced headache.
- 8.1.4 Alcohol-induced headache:
  - 8.1.4.1 Immediate alcohol-induced headache
  - 8.1.4.2 Delayed alcohol-induced headache.
- 8.1.5 Cocaine-induced headache.
- 8.1.6 Histamine-induced headache:
  - 8.1.6.1 Immediate histamine-induced headache
  - 8.1.6.2 Delayed histamine-induced headache.
- 8.1.7 Calcitonin gene-related peptide (CGRP)-induced headache:
  - 8.1.7.1 Immediate CGRP-induced headache
  - 8.1.7.2 Delayed histamine-induced headache.
- 8.1.8 Headache attributed to exogenous acute pressor agent.
- 8.1.9 Headache attributed to occasional use of non-headache medication.
- 8.1.10 Headache attributed to long-term use of non-headache medication.
- 8.1.11 Headache attributed to use of or exposure to other substance.

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methylprednisolone) and antibiotics (monocyclines, tetracyclines, trimethoprim-sulfamethoxazole), and oral contraceptives (ethinylestradiol). Other drugs reported include isotretinoin, danazol, tamoxifen, and isosorbide dinitrate (1,7).

Pathophysiology

The precise mechanisms underlying the development of headache associated with substance use are not well understood. Various pathophysiological abnormalities have been reported: intracranial vasodilation (10), vasoconstrictive effects from noradrenergic alteration in vessel tone due to cocaine (11), altered serotoninergic signal transmission in the brain with abnormal serotonin levels within synapses (12) and frequency of the allelic variant of alcohol dehydrogenase enzyme polymorphism (13) seen in alcohol use, *N*-methyl-D-aspartate receptor dysfunction in analgesic abuse (14), persistent orbitofrontal hypometabolism, and metabolic changes in pain processing structures (15). Headaches can also occur in situations potentially associated with cerebral oedema and intracranial hypertension observed in drugs such as lithium, tamoxifen, cimetidine, indomethacin, antibiotics (tetracycline, monocycline, doxycycline, nalidixic acid, nitrofurantoin, trimethoprim-sulfamethoxazole), vitamin A and retinoids (isotretinoin, all-trans retinoic acid), hormones (thyroxine, human growth hormone, levonorgestrel), and steroids (beclomethasone, methylprednisolone, prednisolone) (7,16). However, these mechanisms do not explain how other drugs that do not penetrate the blood–brain barrier but are frequently implicated in case reports cause headaches. Reviews of the published literature on this are quite limited. Several hypotheses include direct chemically mediated irritative effects on trigeminal afferents, the role of altered neurotransmitter sensitivity in peripheral and central sensitization, as well as a primary cerebral neuronal action, possibly triggering a vascular reaction and subsequent headache (1,9).

Toxic headaches can be induced by acute or delayed exposure to a substance. The immediate headache is closely temporally related to the exposure with onset immediately or within hours, while the delayed headache occurs many hours to days after the immediate headache has resolved. **Box 40.1** list the different headaches attributed to use of or exposure to a substance. In this section, we discuss some of the more common headaches attributed to a substance or its withdrawal.

Box 40.2 ICHD-3 general criteria for headache attributed to a substance

8 Headache attributed to a substance or its withdrawal.
- **A** Headache fulfilling criterion C.
- **B** Use of, exposure to or withdrawal from a substance known to be able to cause headache has occurred.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to use of, exposure to, or withdrawal from the substance
  - **2** Either of the following:
    - (a) Headache has significantly improved or resolved in close temporal relation to cessation of use of or exposure to the substance
    - (b) headache has significantly improved or resolved within a defined period after withdrawal from the substance
  - **3** Headache has characteristics typical for use of, exposure to, or withdrawal from the substance
  - **4** Other evidence exists of causation.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Nitric oxide donor-induced headache

Nitric oxide (NO) donor-induced headache includes those associated with the contact or use of nitroglycerin (NTG), (nitroglycerin headache or dynamite headache) and nitrates or nitrites (hot-dog headache), which may be due to cyclic guanine monophosphate (cGMP) activation (1). NO donors, including amyl nitrate, erythrityl tetranitrate, pentaerythrityl tetranitrate, NTG, isosorbide mono- or dinitrate, sodium nitroprusside, and mannitol hexanitrate, are known to induce both an immediate and delayed type of toxic headache. This type of headache is typically bilateral, frontotemporal, and pulsating. NTG induces immediate headache in most people, but can also cause a delayed headache in patients with migraine or chronic tension-type headache (5,17). These delayed headaches occur, on average, 5–6 hours after exposure. Patients with cluster headache are known to be more susceptible to developing delayed headache only during cluster periods: NTG usually induces a cluster headache attack 1–2 hours after intake (18).

Some susceptible individuals report variable intensity headaches minutes or hours after ingestion of nitrate or nitrites containing food like sausages, other cured meats, and fish (i.e. frankfurters, bacon, ham, salami, pepperoni, corned beef, and pastrami) hence the name 'hot-dog headache' (19). Other nitrite-containing drugs that may trigger headaches include dipyridamole, nimodipine, papaverine hydrochloride, and tolazoline hydrochloride (1).

Phosphodiesterase inhibitor-induced headache

Phosphodiesterase (PDE) inhibitor-induced headache develops within 5 hours of intake of a single dose of PDE inhibitor (i.e. sildenafil, vardenafil, tadalafil, dipyridamole) and resolves spontaneously within 72 hours of onset. PDE-5 inhibitors increase levels of cGMP and/or cyclic adenosine monophosphate. This type of headache has the characteristics of either tension-type headache (bilateral and mild-to-moderate in intensity) or migraine (pulsating and aggravated by physical activity) (1,5).

Carbon monoxide-induced headache

Carbon monoxide (CO)-induced headache is a secondary type of headache, also called warehouse workers' headache, occurring in > 90% (20) of individuals after CO exposure, resolving spontaneously within 72 hours after its elimination. It is usually bilateral, frontal, dull, and continuously discomforting, developing within 12 hours of exposure to CO (20,21). Different levels of exposure to CO, an odourless and colourless gas, cause different clinical symptoms. Carboxyhaemoglobin levels of 10–20% cause a mild headache without gastrointestinal or neurological symptoms; levels of 20–30% cause a moderate pounding headache and irritability; and levels of 30–40% cause a severe headache with nausea, vomiting, and blurred vision. At levels > 40%, headache is usually not a complaint because of the alternation in consciousness (i.e. confusion at 40–50%, coma at 50–60%, and death at 80%) (1,5). One study did suggest that peak intensity of pain did not correlate with the carboxyhaemoglobin levels (20). Common sources of CO poisoning include faulty oil burners or gas cooking appliances in poorly ventilated spaces.

Alcohol-induced headache

Alcohol-induced headache (also referred to as cocktail headache) can begin immediately (within 3 hours), or after a delay (within 5–12 hours; 'hangover headache') following the ingestion of alcohol (usually in the form of alcoholic beverages) (3,22,23). The headache typically resolves within 72 hours after alcohol ingestion (5). Alcohol-induced headache is usually bilateral, pulsating, and aggravated by physical activity. Alcohol-containing beverages can induce headaches within 30–45 minutes after ingestion in susceptible individuals. The effective dose of alcohol to cause alcohol-induced headache is variable, and can be very small in migraineurs. Alcohol is also a well-known trigger of migraine and cluster headaches.

Delayed alcohol-induced headache is one of the commonest types of secondary headache; however, the mechanism of how ethanol causes 'hangover headache' pain remains unclear (24). The alcohol hangover (also termed veisalgia cephalgia) is characterized by headache with or without tremulousness, dryness, pallor, nausea, dizziness, diarrhoea, fatigue, and hyperexcitability combined with decreased occupational, cognitive, or visual–spatial skill performance, which occur several hours after the interruption of the ingestion of alcohol, when the tissue level of the alcohol is low or nil (25). Migraine sufferers are found to experience more severe hangover headaches with less alcohol consumption (5). More than 75% of men and women who have consumed alcohol report that they have experienced hangover at least once, and 15% experience hangovers at least monthly (26). Headaches are a common feature of the syndrome with migraine features including a throbbing quality and aggravated by body movements. So-called vesalgia cephalgia usually lasts 5–10 hours after the alcohol has been metabolized, with an immediate reduction in symptoms with a fresh ingestion of alcohol indicative of possible withdrawal syndrome (1). This syndrome develops when blood alcohol concentration returns to zero and is characterized by a feeling of general misery that may last > 24 hours (27).

The possible mechanisms by which alcohol induces headache include disruption of cerebral autoregulation and decreased cerebral turnover of serotonin, rather than vasodilation (12,28). Alcohol has little or no effect on vascular smooth muscle or cerebral blood flow (1), so that the headache mechanism is likely not related to intra- or extracranial vasodilation. It was also thought that hypomagnesaemia or alcohol additives may participate in inducing the headache. Combining alcohol with other substances such as monoamine oxidase inhibitors, tyramine, disulfiram, metronidazole, furazolidone, chloramphenicol and moxalactam disodium, tolbutamide, or chlorpropamide may cause headache (1).

Maxwell et al. (24) found that direct administration of acetate increased nociceptive behaviours, suggesting that acetate, not acetaldehyde, accumulation results in hangover-like hypersensitivity in a rat model of alcohol hangover. Inhalation of oxygen provides relief of hangover syndrome, which is consistent with the hypothesis that the hangover syndrome is due to a delay in the metabolic recovery of the redox state modified by ingestion of alcohol (1).

Symptoms of hangover may be caused by dehydration, hormonal alterations, dysregulated cytokine pathways, and toxic effects of alcohol. Physiological characteristics include increased cardiac work with normal peripheral resistance, diffuse slowing on electroencephalography, and increased levels of antidiuretic hormone. Effective interventions for hangover headache may include rehydration, prostaglandin inhibitors, and vitamin B6 (25). The section on headache induced by food and/or additives was deleted from the new ICHD-3.

Cocaine-induced headache

Headaches can be provoked by a variety of psychoactive substances, but the exact mechanism is still unknown. Beckmann et al. (8) found that of the 1055 psychoactive substance abusers 27% of patients reported having headache. Eighteen per cent of patients reported having headache attributed to a substance or its withdrawal, and 1.4% had unclassified headache. The most commonly used substances were cannabis (80.5%), alcohol (74.6%), methylamphetamine (18.7%), benzodiazepine (10.4%), volatile solvent (5.8%), cocaine (4.4%), heroin (2.1%), opioids (0.5%), and other substances (1.7%).

The adverse effects of cocaine have been described in the medical literature for over 100 years. Neurological complications related to cocaine use can be classified as neurovascular events (cerebral or spinal, mainly stroke), seizures (generalized or partial), abnormal movements (extrapyramidal symptoms like tics, dystonia), hyperpyrexia, and rhabdomyolysis, as well as miscellaneous complications, including visual loss caused by retinal artery occlusion or optic neuropathy, cardiac events (myocardial infarction, dysrhythmias, aortic dissection,), pregnancy disturbances (pre-eclampsia or eclampsia), psychiatric disturbances (agitation, anxiety, depression, psychosis, paranoia, and suicidal ideation), and headaches (1,29). Cocaine-induced headache is a secondary type of headache occurring within 1 hour of administration of cocaine by any route (oral ('chewing'), intranasal ('snorting'), intravenous ('mainlining'),

and inhalation (smoking)) and resolves within 72 hours. Cocaine-related headaches were reported to be as high as 60–75% in previous studies (11,29). It is typically a moderate-to-severe, bilateral (61–87%), temporal, and pulsating headache that is aggravated by physical activity and associated with phonophobia (73–87%) (5,8). Dhuna et al. (11) identified three patterns of headaches following cocaine use: acute onset of headaches within minutes of cocaine use, increasing headache during a binge, and headaches during abstinence. Migraines were more pronounced in patients using cocaine than in those taking cannabis and alcohol (8). Cocaine-induced headaches begin immediately after drug ingestion, and are usually not associated with nervous system pathology; however, if prolonged and accompanied by focal neurological signs, haemorrhagic or ischaemic stroke or vasculitis should be considered (29,30).

The precise mechanisms underlying the development of headache associated with cocaine are not understood but may be related to the sympathomimetic or vasoconstrictive effects caused by a sudden cocaine surge produced by alkaloidal form of cocaine known as 'crack cocaine' or by the intravenous route by rapidly blocking presynaptic norepinephrine reuptake causing calcium-dependent acute constriction of vascular smooth muscle producing a migraine-like headache, usually with a benign course (1,11,31). Other pathophysiological abnormalities include presynaptic depletion of serotonin, dopamine, and norepinephrine (11).

Histamine-induced headache

Histamine-induced headache is caused immediately (onset at 1 hour and resolves within 1 hour), or after a delay (onset at 2–12 hours and resolves within 72 hours), by acute exposure to histamine administered subcutaneously, by inhalation, or intravenously. This type of headache is usually a bilateral, mild-to-moderate, and pulsating headache that is aggravated by physical activity. Histamine causes an immediate headache in most people, but can also cause a delayed headache in susceptible migraineurs and patients with tension-type headache. These delayed headaches occur, on average, 5–6 hours after exposure. Cluster headache patients develop delayed headache usually 1–2 hours after exposure that is unilateral with associated autonomic features only during cluster periods. The mechanism is primarily mediated via the H_1 receptor, and is almost completely blocked by mepyramine (5).

Calcitonin gene-related peptide-induced headache

Calcitonin gene-related peptide (CGRP) is the most potent vasodilator naturally occurring in the central nervous system, and has long been implicated in the pathophysiology of migraine. Headache induced by CGRP can occur immediately (within 1 hour) after administration by infusion, or after a delay (within 2–12 hours), following acute exposure to CGRP. The headache triggered by CGRP is usually bilateral and mild to moderate in intensity with migraine features (pulsating quality and aggravated by physical activity).

CGRP is a neuropeptide released from activated trigeminal sensory nerves that dilates intracranial blood vessels and transmits vascular nociception. Several studies described this mechanism of CGRP as the rationale for its role in pathophysiology of migraine and using CGRP inhibitors or antibodies in preventing or aborting migraine by showing elevation of CGRP in human external jugular blood during migraine and a drop post-migraine or after treatment with subcutaneous sumatriptan by inhibition of trigeminal CGRP release or CGRP-induced cranial vasodilatation (32,33).

Headache attributed to exogenous acute pressor agent

This is a type of secondary headache disorder occurring during, and caused by, an acute rise in blood pressure induced by an exogenous pressor agent occurring within 1 hour of administration of pressor agent and resolves within 72 hours (5).

Headache attributed to occasional use of non-headache medication

Headache attributed to occasional use of non-headache medication develops as an acute adverse event after occasional use of a medication (onset within minutes to hours of intake and resolves within 72 hours) taken for purposes other than the treatment of headache. These headaches in most cases are dull, continuous, and diffuse with a moderate-to-severe intensity. Headache attributed to occasional use of non-headache medication has been reported as an adverse event after use of many drugs. The following are the most commonly reported drugs: atropine, digitalis, disulfiram, hydralazine, imipramine, nicotine, nifedipine, and nimodipine (5).

Headache attributed to long-term use of non-headache medication

Headache attributed to long-term use of non-headache medication develops as an adverse event during long-term use of a medication taken for purposes other than the treatment of headache. The headache is not necessarily reversible. This type of headache is present on ≥ 15 days per month after long-term use of a medication taken and develops in temporal relation to the commencement of medication intake, or has significantly worsened after an increase in dosage of the medication, or significantly improved or resolved after a reduction in dosage or after stopping the medication that is recognized to cause headache during long-term use (5). The dosage and duration of exposure that may result in headache during long-term use varies for different medications. This headache can be a result of direct pharmacological effect of the medication, such as vasoconstriction producing malignant hypertension, or to a secondary effect such as drug-induced intracranial hypertension. Long-term use of drugs such as anabolic steroids, amiodarone, lithium carbonate, nalidixic acid, thyroid hormone replacement therapy, tetracycline, and minocycline has been reported to potentially, in some users, lead to the development of intracranial hypertension (5).

Headache attributed to use of or exposure to other substance

Headache attributed to use of or exposure to other substance is a secondary type of headache disorder occurring during or soon after, and caused by, use of or exposure to a substance other than those described earlier, including herbal, animal, or other organic or inorganic substances given by physicians or non-physicians with medicinal intent although not licensed as medicinal products. This type of headache develops within 12 hours of exposure and resolves within 72 hours. In most cases this type of headache is dull, diffuse, continuous, and of moderate-to-severe intensity. Headache attributed to use of or exposure to other substance has been reported after exposure to a number of other organic and inorganic substances. The ICHD-3 notes that the most commonly reported agents include inorganic compounds (arsenic, borate, bromate, chlorate, copper,

iodine, lead, lithium, mercury, tolazoline hydrochloride) and organic compounds (aniline, balsam, camphor, carbon disulfide, carbon tetrachloride, chlordecone, ethylenediaminetetraacetic acid, heptachlor, hydrogen sulfide, kerosene, long-chain alcohols, methyl alcohol, methyl bromide, methyl chloride, methyl iodine, naphthalene, organophosphorous compounds (parathion, pyrethrum)) (5).

Management

Ideally, the approach to the management of headaches attributed to substance use are as follows: (i) identify the clinical syndrome; (ii) stop further exposure to the substance immediately; and (iii) advise the patient to avoid contact with the substance or substances in the future. Realistically, this is not always possible as the medication in question may be required; however, typically, alternate options can be substituted.

Specific treatments may be available depending on the impugned substance in question. Pure or hyperbaric oxygen is given to treat CO intoxication. Ergotamine has been shown to have the potential abort headaches induced by NTG in many individuals. Injectable sumatriptan can terminate the delayed headache induced by an NO donor (1).

The prognosis of headaches associated with acute use of substances, in general, is good with the spontaneous resolution of symptoms after exposure stops; however, excessive exposure to some substances (i.e. CO) can be lethal as can excessive use of illicit drugs (particularly those containing contaminants or combinations with other substances such as crack or amphetamine analogues) (1).

Headaches attributed to disorders of homeostasis

Headaches attributed to disorders of homeostasis were referred to as 'headaches associated with metabolic or systemic diseases' in the first edition of the ICHD (34). The most recent version (ICHD-3) states that if a headache occurs for the first time in close temporal relation to a disorder of homoeostasis, it is coded as a secondary headache attributed to that disorder specifically (even when the new headache has the characteristics of any of the primary headache disorders) (5). The headaches attributed to disorders of homeostasis include headaches attributed to (i) hypoxia and/or hypercapnia (high altitude, diving, sleep apnoea); (ii) dialysis; (iii) arterial hypertension (phaeochromocytoma, hypertensive crisis without hypertensive encephalopathy, hypertensive encephalopathy, pre-eclampsia or eclampsia, autonomic dysreflexia); (iv) hypothyroidism; (v) fasting; (vi) cardiac cephalalgia; and (vii) other disorder of homoeostasis. Although there are varied mechanisms behind causation of these different subtypes of headache attributed to disorder of homoeostasis (10.0), there are general diagnostic criteria applicable in most cases as seen in **Box 40.3** (5,35).

Headache attributed to hypoxia or hypercapnia

This is a group of headache disorders caused by hypoxia and/or hypercapnia and occurring in conditions of exposure to one or both. It is difficult to separate the effects of hypoxia and hypercapnia (**Box 40.4**). The ICHD-2 criteria for headache secondary to hypoxia state that headache begins within 24 hours after acute onset of hypoxia with a partial pressure of oxygen (PaO_2) < 70 mmHg or in chronically hypoxic patients with a PaO_2 persistently at or below these levels; the ICHD-3 does not specify the parameters for the hypoxia/hypercapnia. Diseases that are related to acute or chronic hypoxia/hypercapnia may be associated with headache. Any disease that induces a hypoxic state, such as pulmonary diseases (asthma, chronic obstructive pulmonary disease), cardiac disease (congestive heart failure), or haematological disorders (with significant anaemia), may be associated with headache.

There are four unique situations associated with headaches attributed to hypoxia that are common, potentially manageable, and cited in the ICHD-3. These entities include headaches attributed to high altitude, airplane travel, diving, and sleep apnoea, and each will be discussed in detail in this section.

Box 40.3 Headache attributed to a disorder of homoeostasis

- **A** Headache fulfilling criterion C.
- **B** A disorder of homoeostasis known to be able to cause headache has been diagnosed.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of the disorder of homoeostasis
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with worsening of the disorder of homoeostasis
    - (b) Headache has significantly improved after resolution of the disorder of homoeostasis
  - **3** Headache has characteristics typical for the disorder of homoeostasis.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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High altitude headache

ICHD-3 defines high-altitude headache as typically a bilateral headache, aggravated by exertion, and caused by ascent above 2500 metres, which resolves spontaneously within 24 hours after descent (**Box 40.5**). Although the criteria suggest that the headaches are more often bilateral, unilateral headaches can occur, and this is seen more often in migraineurs (36).

Headache is the most frequent symptom of acute exposure to high altitude, with an incidence as high as 73.3–86.7% (37–39). High-altitude headache is often associated with nausea, photophobia, vertigo, and poor concentration. In severe cases, impaired judgement and symptoms or signs suggestive of brain oedema can occur. Risk

Box 40.4 Headache attributed to hypoxia or hypercapnia

- **A** Any headache fulfilling criterion C.
- **B** Exposure to conditions of hypoxia and/or hypercapnia.
- **C** Evidence of causation demonstrated by either or both of the following:
  - **1** Headache has developed in temporal relation to the exposure
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with increasing exposure to hypoxia and/or hypercapnia
    - (b) Headache has significantly improved in parallel with improvement in hypoxia and/or hypercapnia.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 40.5 Headache attributed to high altitude

- **A** Headache fulfilling criterion C.
- **B** Ascent to altitude above 2500 metres has occurred.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the ascent
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with continuing ascent
    - (b) Headache has resolved within 24 hours after descent to below 2500 metres
  - **3** Headache has at least two of the following three characteristics:
    - (a) Bilateral location
    - (b) Mild or moderate intensity
    - (c) Aggravated by exertion, movement, straining, coughing, and/or bending.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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factors for high-altitude headache include a history of migraine, low arterial oxygen saturation, high perceived degree of exertion, fluid intake < 2 L within 24 hours, insomnia, high heart rate and high Self-Rating Anxiety Scale score (36,37).

Like many headaches associated with disorders of homeostasis, the precise pathophysiological process that causes high-altitude headache remains unknown. Hypoxia elicits neurohumoral and haemodynamic responses that result in over-perfusion of microvascular beds, increased hydrostatic capillary pressure, capillary leakage, and consequent oedema (40). Several neuroimaging studies have demonstrated a mild increase in brain volume associated with an increased T2 relaxation time and apparent diffusion coefficient that were consistently associated with the severity of neurological symptoms. The authors suggested that the brain oedema is predominantly vasogenic (with movement of fluid and proteins out of the vascular compartment into extracellular brain areas) rather than a cytotoxic oedema (due to cellular swelling). Mild extracellular vasogenic oedema contributes to the generalized brain swelling observed at high altitude, and may be of significance in headache attributed to altitude (41). This was supported by findings that elderly people have fewer headaches than younger people after exposure to high altitude, probably due to a certain degree of brain atrophy (42).

A recent study examined indices of brain white matter water mobility after 2 and 10 hours in normoxia (21% O_2) and hypoxia (12% O_2) using magnetic resonance imaging (MRI) whole-brain analysis (tract-based spatial statistics). The results of this study indicate that acute periods of hypoxaemia cause a shift of water into the intracellular space within the cerebral white matter, which were found to be related to the intensity of high-altitude headache, whereas no evidence of brain oedema (a volumetric enlargement) is identifiable (43). Furthermore, efforts to demonstrate a specific genotype associated with a predisposition to develop this headache led to the suggestion that low mRNA expression of the ATP1A1 subunit of the ATPase gene may be of importance (44).

Medical treatment of headaches attributed to high altitude involves simple analgesics such as paracetamol (acetaminophen) or ibuprofen, antiemetic agents, as well as acetazolamide, at 125–250 mg twice daily ± dexamethasone (45–47). Randomized, placebo-controlled trials also showed a significant reduction in the risk of headache with the use of acetylsalicylic acid at a dose of 320 mg taken three times at 4-hour intervals, starting 1 hour before ascent (28), or ibuprofen at a dose of 600 mg three times daily (48,49), starting a few hours before ascent to altitudes between 3480 and 4920 metres. In a recent systematic review and meta-analysis of three randomized controlled trials showed that ibuprofen seems efficacious (with absolute risk reduction of 15% and number needed to treat of seven for the prevention of high-altitude headache (47). Important non-pharmacological strategies include 2 days of acclimatization prior to engaging in strenuous exercise at high altitudes, slow ascent, liberal fluid intake, and avoidance of alcohol (46).

Headache attributed to airplane travel

Headache attributed to airplane travel (**Box 40.6**), also called 'airplane headache' (AH), is a new addition to the ICHD classification criteria, first introduced in ICHD-3 (see also Chapter 56). This headache is often severe, usually unilateral and periocular, and without autonomic symptoms, occurring during and caused by airplane travel and it remits after landing (5). The largest case series of AH reported a rather stereotyped nature of the attacks, which include the short duration of pain (lasting < 30 minutes in up to 95% of cases), a clear relationship with the landing phase, a male preponderance, and the absence of accompanying signs and/or symptoms (50). AH occurs in up to 8.3% of Scandinavian air travellers, according to a recent study (51), and during landing in > 85–90% of patients (51,52). Although the pathophysiology of AH remains unclear, speculation exists that the inflammation squeeze effect on the frontal sinus wall, when air trapped inside it contracts, producing a negative pressure leading to mucosal oedema, transudation, and intense pain (53). Another proposed theory is that this type of headache generally results from the temporary local inflammation caused by hypoxia or dryness in the sinus mucosa or sinus barotraumas (54). The most recent systematic review on AH showed that the most common theoretical mechanism in the development of AH include changes in cabin pressure during take-off and landing, which lead to sinus barotrauma and local inflammation (prostaglandin E2 (PGE-2) is found to be a potential biomarker for AH), as well as possibly vasodilation in the cerebral arteries (55,56).

There are no specific guidelines for the treatment of AH because this type of headache is considered short-lasting and aborted after the flight travel is over. Prophylactic therapy for AH may include trials of simple analgesics, NSAIDs, antihistamines, triptans, and

Box 40.6 Headache attributed to airplane travel

- **A** At least two episodes of headache fulfilling criterion C.
- **B** The patient is travelling by airplane.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed during the aeroplane flight
  - **2** Either or both of the following:
    - (a) Headache has worsened in temporal relation to ascent following take-off and/or descent prior to landing of the aeroplane
    - (b) Headache has spontaneously improved within 30 minutes after the ascent or descent of the aeroplane is completed
  - **3** Headache is severe, with at least two of the following three characteristics:
    - (a) Unilateral location
    - (b) Orbitofrontal location
    - (c) Jabbing or stabbing quality.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 40.7 Diving headache

- **A** Any headache fulfilling criterion C.
- **B** Both of the following:
  - **1** The patient is diving at a depth > 10 metres
  - **2** No evidence of decompression illness.
- **C** Evidence of causation demonstrated by at least one of the following:
  - **1** Headache has developed during the dive
  - **2** Either or both of the following:
    - (a) Headache has worsened as the dive is continued
    - (b) Either of the following:
      - (i) Headache has spontaneously resolved within 3 days of completion of the dive
      - (ii) Headache has remitted within 1 hour after treatment with 100% oxygen
  - **3** At least one of the following symptoms of CO_2 intoxication:
    - (a) Mental confusion
    - (b) Light-headedness
    - (c) Motor incoordination
    - (d) Dyspnoea
    - (e) Facial flushing.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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nasal decongestants administered 30 minutes up to 1 hour prior to travel (52,53,55,56). Among these medications, ibuprofen, naproxen, and triptans (sumatriptan, naratriptan, zolmitriptan, and eletriptan have been found the most effective (55); however, there is a need to perform randomized controlled trials in pharmacological treatments for AH. Performing specific active spontaneous manoeuvres (i.e. pressure on the pain area, Valsalva manoeuvres, relaxation methods, chewing, and extension of the earlobe) has been shown to decrease the pain intensity (52,57).

The most common symptoms of AH include severe, short lasting (< 30 minutes in most cases) unilateral, throbbing, or stabbing headache over the fronto-orbital area with parietal spread, which can side-shift between different flights in 10% of cases, autonomic features like restlessness and unilateral tearing, and migraine features like nausea, photophobia, and phonophobia (51,55,56).

Diving headache

Diving headache (Box 40.7)is a headache caused by diving below 10 metres, occurring during the dive and often intensified on resurfacing, in the absence of decompression illness. It is usually accompanied by symptoms of carbon dioxide (CO_2) intoxication. It remits quickly with oxygen or, if this is not given, spontaneously within 3 days after the dive has ended (5). The best clinical example of headache attributed to hypercapnia is diving headache. There is some evidence that hypercapnia (arterial partial pressure of CO_2 (pCO_2) > 50 mmHg) is known to cause relaxation of cerebrovascular smooth muscle, leading to intracranial vasodilatation and increased intracranial pressure leading to headache (57,58). CO_2 may accumulate in a diver who intentionally holds his or her breath intermittently (skip breathing) in a mistaken attempt to conserve air, or takes shallow breaths to minimize buoyancy variations in the narrow passages of a wreck or cave. Divers may also hypoventilate unintentionally when a tight wetsuit or buoyancy compensator jacket restricts chest wall expansion, or when ventilation is inadequate in response to physical exertion. Notably, strenuous exercise increases the rate of CO_2 production more than 10-fold, resulting in a transient elevation of pCO_2 to > 60 mmHg. Inadequate ventilation of compressed gases can lead to CO_2 accumulation, cerebral vasodilation, and headache (57,58). Diving headache usually intensifies during the decompression phase of the dive or on resurfacing.

Notably, a study by Di Fabio et al. (59) suggested that the prevalence of headache among male divers and matched controls was not significant (16% vs 22%) and concluded that scuba diving is not associated with headache.

It is well established that headache in divers, although uncommon (4.5–23%) and relatively benign, can occasionally signify serious consequences of hyperbaric exposure, such as arterial gas embolism, decompression sickness, and otic or paranasal sinus barotrauma (60–62). For patients in whom the headache is not obviously benign, the diagnostic evaluation should consider otic and paranasal sinus barotrauma, arterial gas embolism, decompression sickness, CO_2 retention, CO toxicity, hyperbaric-triggered migraine, cervical and temporomandibular joint strain, supraorbital neuralgia, carotid artery dissection, and exertional and cold stimulus headache syndromes (57). Focal neurological symptoms, even in the migraineur, should not be ignored, but rather treated with 100% oxygen acutely, and the patient should be referred without delay to a facility with a hyperbaric chamber (35). Interestingly, a relationship between patent foramen ovale and migraine with aura was first observed in scuba divers (63). In 2015, the South Pacific Underwater Medicine Society (SPUMS) and the United Kingdome Sports Diving Medical Committee (UKSDMC) published joint guidelines recommending that screening for PFO using a bubble contrast transthoracic echocardiography with provocative manoeuvres should be considered in divers with high risk factors, including a history of migraine with aura, cerebral, spinal, inner ear or cutaneous decompression illness, a family history of PFO or atrial septal defect or those with other forms of congenital heart disease (58,64).

Sleep apnoea headache

Sleep apnoea headache (Box 40.8) is a recurrent morning headache, usually bilateral and typically with a duration of less than 4 hours,

Box 40.8 Headache attributed to sleep apnoea

- **A** Headache present on awakening after sleep and fulfilling criterion C.
- **B** Sleep apnoea with apnoea–hypopnoea index ≥ 5 has been diagnosed.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of sleep apnoea
  - **2** Either or both of the following:
    - (a) Headache has worsened in parallel with worsening of sleep apnoea
    - (b) Headache has significantly improved or remitted in parallel with improvement in or resolution of sleep apnoea
  - **3** Headache has at least one of the following three characteristics:
    - (a) Recurring on ≥ 15 days/month
    - (b) All of the following:
      - (i) Bilateral location
      - (ii) Pressing quality
      - (iii) Not accompanied by nausea, photophobia or phonophobia.
    - (c) Resolving within 4 hours.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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caused by sleep apnoea diagnosed using polysomnography with an apnoea–hypopnoea index (AHI) ≥ 5. AHI is calculated by dividing the number of apnoeic events by the number of hours of sleep (5). Importantly, this headache disorder resolves with successful treatment of the sleep apnoea (65,66).

The relationship between headache and sleep disorders is complex and incompletely understood (see also Chapter 57). Firstly, sleep disturbances may trigger migraine (67). Secondly, snoring and other sleep disorders are risk factors for migraine progression (68) Thirdly, sleep apnoea is a risk factor for cluster headache and morning headaches (69,70). Although morning headache is significantly more frequent in patients with obstructive sleep apnoea (OSA) (11.8% vs 4.6%) than those without OSA, headache present on awakening is a non-specific symptom that occurs in a variety of primary and secondary headache disorders, in sleep-related respiratory disorders other than sleep apnoea (e.g. Pickwickian syndrome, chronic obstructive pulmonary disease), and in other primary sleep disorders such as periodic leg movements of sleep (71).

Studies have demonstrated higher prevalence (27.2–74%) of morning headaches in patients with OSA (66,72–74), habitual snoring (23.5%) (72), and insomnia (48%). Other predictors for sleep apnoea headache include female sex, history of migraine, psychological distress, and obesity (72,74).

The exact pathophysiology of sleep apnoea headache remains debatable. Several possible mechanisms include hypoxia or oxygen desaturation, hypercapnia, or disturbance in sleep architecture (i.e. shorter rapid eye movement sleep), as well as increase in intracranial pressure (66,72–74).

Dialysis headache

Dialysis headache (Box 40.9) is a type of secondary headache disorder with no specific characteristics occurring during or after (most often after the second hour) haemodialysis (35,75,76). It resolves spontaneously within 72 hours after the haemodialysis session has ended or headache episodes may also stop altogether after a successful kidney transplant and termination of haemodialysis (5). Dialysis headache occurs in 27–73% of patients receiving haemodialysis (76–79. However, in a prospective study, around one-third of patients with otherwise typical dialysis headache also had similar headache in between their dialysis sessions and the headaches occurred mainly in the second half of the haemodialysis (86%) (77). This type of headache is described as a mild to moderate (73%), bifronto-temporal (50%) ache, which can escalate to severe throbbing (87%) pain lasting for < 4 hours (63%), that worsens in the reclined position and is accompanied by nausea and vomiting (76).

There is no consensus on pathophysiology of dialysis headache; however, it thought to commonly occur in association with hypotension and dialysis disequilibrium syndrome. Dialysis disequilibrium syndrome may begin as a headache and then progress to obtundation and coma, with or without seizures. The most consistent triggers for dialysis headache found in several studies include arterial hypertension (38%), arterial hypotension (12%), and changes in weight during the haemodialysis sessions (79,80). Reduced serum osmolality, low magnesium, and high sodium levels may also be risk factors for developing dialysis headache (78). Variations in NO, CGRP, and substance P levels related to dialysis pose another potential contributor to dialysis headache (76).

Dialysis headache may be prevented by changing dialysis parameters. There is no specific treatment for dialysis headache. Acute treatment is mainly symptomatic and complicated by the chronic renal insufficiency status. Analgesics and NSAIDs are often used during dialysis sessions. The use of preventative medication may be necessary to improve headache burden; however, evidence for this is very limited. Angiotensin-converting enzyme inhibitors were given in one case, with a good response reported (81).

Headache attributed to hypertension

Headache attributed to hypertension (Box 40.10) is caused by arterial hypertension, usually during an acute rise in systolic (to ≥ 180 mmHg) and/or diastolic (to ≥ 120 mmHg) blood pressure. The headache is often bilateral and pulsating. The headache remits after normalization of blood pressure. Mild (140–159/90–99 mmHg) or moderate (160–179/100–109 mmHg) chronic arterial hypertension does not appear to cause headache. Some studies have suggested that ambulatory blood pressure monitoring in patients with mild and moderate hypertension has demonstrated no convincing relationship between blood pressure fluctuations over a 24-hour period and the presence or absence of headache (82,83). Others report a significant correlation between blood pressure levels and headache, as well as reduced headache frequency with treatment of hypertension (84–86). Whether moderate hypertension predisposes to headache at all remains unclear.

Several studies have documented association of headache with phaeochromocytoma (87–90), hypertensive encephalopathy (91,92), pre-eclampsia and eclampsia (93,94), as well as autonomic

Box 40.9 Dialysis headache

- **A** At least three episodes of acute headache fulfilling criterion C.
- **B** The patient is on haemodialysis.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Each headache has developed during a session of haemodialysis
  - **2** Either or both of the following:
    - (a) Each headache has worsened during the dialysis session
    - (b) Each headache has resolved within 72 hours after the end of the dialysis session
  - **3** Headache episodes cease altogether after successful kidney transplantation and termination of haemodialysis.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 40.10 Headache attributed to hypertension

- **1** Any headache fulfilling criterion C
- **2** Hypertension, with systolic pressure ≥180 mm Hg and/or diastolic pressure ≥120 mm Hg, has been demonstrated
- **3** Evidence of causation demonstrated by either or both of the following:
  - **1** Headache has developed in temporal relation to the onset of hypertension
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with worsening hypertension
    - (b) Headache has significantly improved in parallel with improvement in hypertension
  - **3** Not better accounted for by another ICHD-3 diagnosis.

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dysreflexia (95). The proposed mechanism for this type of headache is failure of the normal baroreceptor reflex (85).

Headache attributed to phaeochromocytoma

Headaches attributed to phaeochromocytoma (Box 40.11) are usually severe and of short duration (< 1 hour) with attacks accompanied by sweating, palpitations, pallor, and/or anxiety (5). This type of headache occurs as a paroxysmal headache in 51–80% of patients with phaeochromocytoma (87,88). The headache is often severe, frontal or occipital, and usually described as either pulsating or constant in quality. A notable feature of the headache is its short duration: < 15 minutes in 50% and < 1 hour in 70% of patients (87). Associated features include apprehension and/or anxiety, often with a sense of impending death, tremor, visual disturbances, abdominal or chest pain, nausea, vomiting, facial flushing, and, occasionally, paraesthesia (87,89). The diagnosis of phaeochromocytoma is established by the demonstration of increased excretion of catecholamines or catecholamine metabolites, and can usually be secured by analysis of a single 24-hour urine sample collected when the patient is hypertensive or symptomatic (87,89,90). The variable duration and intensity of the headache correlates with the pressor and cranial vasoconstrictor effects of the secreted amines (89).

Headache attributed to hypertensive crisis without hypertensive encephalopathy

Headache attributed to hypertensive crisis (Box 40.12) without hypertensive encephalopathy is usually a bilateral and pulsating headache, caused by a paroxysmal rise of arterial hypertension (systolic ≥ 180 mmHg and/or diastolic ≥ 120 mmHg). It remits after normalization of blood pressure (5). Paroxysmal hypertension may occur in association with failure of baroreceptor reflexes (after carotid endarterectomy or subsequent to irradiation of the neck) or in patients with enterochromaffin cell tumours.

Box 40.11 Headache attributed to phaeochromocytoma

- **A** Recurrent discrete short-lasting headache episodes fulfilling criterion C.
- **B** Phaeochromocytoma has been demonstrated.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache episodes have commenced in temporal relation to development of the phaeochromocytoma, or led to its discovery
  - **2** Either or both of the following:
    - (a) Individual headache episodes develop in temporal relation to abrupt rises in blood pressure
    - (b) Individual headache episodes remit in temporal relation to normalization of blood pressure
  - **3** Headache is accompanied by at least one of the following:
    - (a) Sweating
    - (b) Palpitations
    - (c) Anxiety
    - (d) Pallor
  - **4** Headache episodes remit entirely after removal of the phaeochromocytoma.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 40.12 Headache attributed to hypertensive crisis without hypertensive encephalopathy

- **A** Headache fulfilling criterion C.
- **B** Both of the following:
  - **1** A hypertensive crisis is occurring
  - **2** No clinical features or other evidence of hypertensive encephalopathy.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed during the hypertensive crisis
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with increasing hypertension
    - (b) Headache has significantly improved or resolved in parallel with improvement in or resolution of the hypertensive crisis
  - **3** Headache has at least one of the following three characteristics:
    - (a) Bilateral location
    - (b) Pulsating quality
    - (c) Precipitated by physical activity.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Headache attributed to hypertensive encephalopathy

Headache attributed to hypertensive encephalopathy (Box 40.13) consists of a headache (usually bilateral and pulsating), caused by persistent blood pressure elevation to 180/120 mmHg or above and accompanied by symptoms of encephalopathy such as confusion, lethargy, visual disturbances, or seizures. It improves after normalization of blood pressure (5). Hypertensive encephalopathy presents with persistent elevation of blood pressure to ≥ 180/120 mmHg and at least two of confusion, reduced level of consciousness, visual disturbances including blindness, and seizures (91,92). Headache is one of the most frequent signs (22%) at presentation in hypertensive urgencies (92). It is thought to occur when compensatory cerebrovascular vasoconstriction can no longer prevent cerebral

Box 40.13 Headache attributed to hypertensive encephalopathy

- **A** Headache fulfilling criterion C.
- **B** Hypertensive encephalopathy has been diagnosed.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of the hypertensive encephalopathy
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with worsening of the hypertensive encephalopathy
    - (b) Headache has significantly improved or resolved in parallel with improvement in or resolution of the hypertensive encephalopathy.
  - **3** Headache has at least two of the following three characteristics:
    - (a) Diffuse pain
    - (b) Pulsating quality
    - (c) Aggravated by physical activity.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 40.14 Headache attributed to pre-eclampsia or eclampsia

- **A** Headache, in a woman who is pregnant or in the puerperium (up to 4 weeks postpartum), fulfilling criterion C.
- **B** Pre-eclampsia or eclampsia has been diagnosed.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of the pre-eclampsia or eclampsia
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with worsening of the pre-eclampsia or eclampsia
    - (b) Headache has significantly improved or resolved in parallel with improvement in or resolution of the pre-eclampsia or eclampsia
  - **3** Headache has at least two of the following three characteristics:
    - (a) Bilateral location
    - (b) Pulsating quality
    - (c) Aggravated by physical activity.

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Box 40.15 Headache attributed to autonomic dysreflexia

- **A** Headache of sudden onset, fulfilling criterion C.
- **B** Presence of spinal cord injury and autonomic dysreflexia documented by a paroxysmal rise above baseline in systolic pressure of ≥30 mm Hg and/or diastolic pressure of ≥ 20 mm Hg.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the rise in blood pressure
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with increase in blood pressure
    - (b) Headache has significantly improved in parallel with decrease in blood pressure
  - **3** Headache has at least two of the following four characteristics:
    - (a) Severe intensity
    - (b) Pounding or throbbing (pulsating) quality
    - (c) Accompanied by diaphoresis cranial to the level of the spinal cord injury
    - (d) Triggered by bladder or bowel reflexes.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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hyperperfusion as blood pressure rises (96). As normal cerebral autoregulation of blood flow is overwhelmed, endothelial permeability increases and cerebral oedema occurs (91). On MRI, this is often most prominent in the parieto-occipital white matter (97). Although hypertensive encephalopathy in patients with chronic arterial hypertension is usually accompanied by a diastolic blood pressure of > 120 mmHg, and by grade III or IV hypertensive retinopathy (Keith–Wagener–Barker classification), previously normotensive individuals can, occasionally, develop signs of encephalopathy with blood pressures as low as 160/100 mmHg (98).

Headache attributed to pre-eclampsia or eclampsia

Headache attributed to pre-eclampsia or eclampsia (**Box 40.14**) is usually a bilateral and pulsating headache, occurring in women with pre-eclampsia or eclampsia during pregnancy or the immediate puerperium (99). It remits after resolution of the pre-eclampsia or eclampsia (5). Pre-eclampsia and eclampsia appear to involve a strong maternal inflammatory response, with broad immunological systemic activity (93). The diagnosis of pre-eclampsia and eclampsia require hypertension (> 140/90 mmHg) documented on two blood pressure readings at least 4 hours apart, or a rise in diastolic pressure of ≥ 15 mmHg or in systolic pressure of ≥ 30 mmHg, coupled with urinary protein excretion > 0.3 g/24 hours for diagnosis. They are considered as multisytemic disorders that may present with tissue oedema, thrombocytopenia, and abnormalities in liver function (93), as well as seizures in patients with eclampsia. A case–control study found that headache was significantly more frequent in patients with pre-eclampsia (63%) than in controls (25%) (odds ratio 4.95, 95% confidence interval 2.47–9.92) (100).

Headache attributed to autonomic dysreflexia

Headache attributed to autonomic dysreflexia (**Box 40.15**) is a throbbing, severe headache, in patients with spinal cord injury (SCI) and autonomic dysreflexia (5). It is a sudden-onset type of severe headache associated with sudden increase in blood pressure, altered heart rate, and diaphoresis cranial to the level of SCI (95). Severe headaches occur in 56–85% of the patients with autonomic dysreflexia (101,102). Triggers include noxious or non-noxious stimuli, usually of visceral origin (bladder distension, urinary tract infection, bowel distension or impaction, urological procedures, gastric ulcer, and others), but also of somatic origin (pressure ulcers, ingrown toenail, burns, trauma, or surgical or invasive diagnostic procedures) (102). The time to onset of autonomic dysreflexia after SCI is variable and has been reported to be from 4 days to 15 years (101). The most important predictors of autonomic dysreflexia are the level and severity of SCI. Patients with complete SCI are at greater risk of development of autonomic dysreflexia and, consequently, more susceptible to develop headaches (95). Little is known about the mechanism of headache attributed to autonomic dysreflexia; however, it has been postulated that this type of headache has a vasomotor nature and may result from passive dilation of cerebral vessels or increased circulating PGE-2 (95). Given that autonomic dysreflexia can be a life-threatening condition, its prompt recognition and appropriate management are critical. The primary treatment of this type of autonomic headache involves management of actual episode of autonomic dysreflexia, which includes close monitoring of blood pressure and heart rate as the following steps are followed: (i) patient is placed in a sitting position; (ii) removal/loosening of clothing or constrictive devices; (iii) scrutinize for potential triggers (i.e. bladder distension and bowel impaction); (iv) pharmacological treatment with a rapid-onset and short-duration antihypertensive agent (i.e. nifedipine or nitrates) for elevated systolic blood pressure (≥ 150 mmHg) (95).

Headache attributed to hypothyroidism

Headache attributed to hypothyroidism (**Box 40.16**) is usually bilateral and non-pulsatile, occurring in patients with hypothyroidism and remitting after normalization of thyroid hormone levels (5,103) occurring in approximately 30% of patients with hypothyroidism with female preponderance (103,104). In migraineurs with subclinical hypothyroidism, treatment of borderline hypothyroidism is

Box 40.16 Headache attributed to hypothyroidism

- **A** Headache fulfilling criterion C.
- **B** Hypothyroidism has been demonstrated.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of the hypothyroidism, or led to its discovery
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with worsening of the hypothyroidism
    - (b) Headache has significantly improved or resolved in parallel with improvement in or resolution of the hypothyroidism
  - **3** Headache has either or both of the following characteristics:
    - (a) Bilateral location
    - (b) Constant over time.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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sometimes followed by dramatic improvement in the control of the headache (105). This type of headache is described as intermittent, unilateral, throbbing pain associated with nausea and/or vomiting, which begins within 2 months of the onset of hypothyroidism and lasts < 3 months after its effective treatment (106). The mechanism of headache attributed to thyroid disease is unclear. There is a female preponderance and often a history of migraine in childhood.

Hypothyroidism has also been identified as a potential risk factor for new daily persistent headache in a clinic-based case–control study, when the control group was migraine (105). In the presence of hypothyroidism, it is important to remember that headache can also be a manifestation of pituitary adenoma (107).

Headache attributed to fasting

Headache attributed to fasting (Box 40.17) is typically a diffuse non-pulsating headache, usually mild to moderate, occurring during and caused by fasting for at least 8 hours that is relieved after eating (see also Chapter 7) (5). Even though the typical headache attributed to fasting is diffuse, non-pulsating, and mild to moderate in intensity, in those with a prior history of migraine the headache may resemble migraine without aura (108).

The aetiology of fasting induced headaches is uncertain (109). A commonly reported migraine triggers is hypoglycaemia. Headache attributed to fasting is significantly more common in people who have a prior history of headache, particularly migraine. However, in individuals without a well-defined history of headache, prolonged fasting may also be associated with the development of headaches.

Box 40.17 Headache attributed to fasting

- **A** Diffuse headache not fulfilling the criteria for '1. Migraine' or any of its types but fulfilling criterion C below.
- **B** The patient has fasted for ≥ 8 hours.
- **C** Evidence of causation demonstrated by both of the following:
  - **1** Headache has developed during fasting
  - **2** Headache has significantly improved after eating.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 40.18 Cardiac cephalalgia

- **A** Any headache fulfilling criterion C.
- **B** Acute myocardial ischaemia has been demonstrated.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of acute myocardial ischaemia
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with worsening of the myocardial ischaemia
    - (b) Headache has significantly improved or resolved in parallel with improvement in or resolution of the myocardial ischaemia.
  - **3** Headache has at least two of the following four characteristics:
    - (a) Moderate-to-severe intensity
    - (b) Accompanied by nausea
    - (c) Not accompanied by photophobia or phonophobia
    - (d) Aggravated by exertion
  - **4** Headache is relieved by nitroglycerin or its derivatives.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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This is often seen in prolonged religious fasting and has been documented as 'Yom Kippur headache' (110) and 'first of Ramadan headache' (49). The likelihood of headache developing as a result of a fast increases with the duration of the fast. Fasting headache can occur in the absence of hypoglycaemia, suggesting that other factors play an important role (e.g. caffeine withdrawal, duration of sleep, and circadian factors).

In terms of treatment, a recent study suggested that pre-emptive cyclooxygenase 2 (COX-2) inhibitor treatment (rofecoxib, 50 mg just before the onset of fasting) is effective in reducing these forms of headache, similar to its effect in menstrual migraine (108). Because COX-2 inhibitors are not available in many countries, pre-emptive treatment with NSAIDs or long-acting triptans may be a reasonable option (110).

Cardiac cephalalgia

Cardiac cephalalgia (Box 40.18) is a headache with migraine features, usually but not always aggravated by exercise, occurring during an episode of myocardial ischaemia that is relieved by NTG (see also Chapter 28) (5). Lipton et al. (111) proposed that this type of headache is a rare and treatable form of exertional headache. During a stress test in two subjects, typical headaches correlated with electrocardiography changes indicative of myocardial ischaemia. In both patients, coronary angiography revealed three-vessel disease, and myocardial revascularization procedures were followed by complete resolution of headaches.

ICHD-3 states that the diagnosis must include careful and detailed headache history and simultaneous cardiac ischaemia during treadmill or nuclear cardiac stress testing. However, cardiac cephalalgia occurring at rest has been described (112). Several authors reported that this type of headache may be the sole manifestation of myocardial ischaemia (112–115). A recent literature review of cardiac cephalalgia showed that in more than half of the 35 reviewed cases, the headache was triggered by high myocardial oxygen consumption (i.e. exertion, sexual activity, and emotional fluctuation); however, in six cases the headache occurred during rest. Appropriate and timely diagnosis of cardiac cephalalgia is necessary to avoid serious

consequences (115). Cardiac cephalalgia, like migraine, can present with severe headaches associated with photophobia, phonophobia, osmophobia, nausea, or vomiting, and triggered by exertion (116). It is therefore crucial to distinguish this disorder from migraine without aura, particularly as vasoconstrictor medications (e.g. triptans, ergots) are indicated in the treatment of migraine but contraindicated in patients with ischaemic heart disease.

The mechanisms involved in cardiac cephalalgia remain unclear as this diagnosis was introduced in 1997. However, possible mechanisms reported are related to neural convergence, including somatic and sympathetic impulses converging in the posterior horn of the spinal cord, mixing neural supply to cervical area and cranial vessels; transient increases of intracardiac pressure that cause intracranial pressure elevation and severe headache; and a functioning ventricular pacemaker producing the headache (35,113). A recent case report of cardiac cephalalgia confirmed evidence of cerebral hypoperfusion, which is the new proposed mechanism for this type of headache, including reversible cerebral vasoconstriction and possible sympathetic hyperfunction through activation of cardiac sympathetic afferents during myocardial ischaemia, which can increase the sympathetic outflow through cardiac sympathetic nerve reflexes, as well as abnormal hypothalamic functional connectivity (116).

Headache attributed to other disorder of homoeostasis

Headache attributed to another disorder of homoeostasis (Box 40.19) is caused by any disorder of homoeostasis not described thus far. Although relationships between headache and a variety of systemic and metabolic diseases have been proposed, systematic evaluation of these relationships has not been performed and there is insufficient evidence on which to build operational diagnostic criteria (5).

Headache attributed to systemic infection

Headache attributed to systemic infection is a secondary type of headache disorder, which occurs for the first time in close temporal relation to an infection (11). Other terms used include fever-related headache, headache caused by microorganisms, toxaemic headache, septicaemic headache, or headache as part of the infectious disease syndrome (117). It is usually the consequence of active infection, resolving within 3 months of eradication of the infection (11). Depending on the pathogenic agent, the infection may not be able to be effectively eradicated and as long as the infection remains active the headache may not resolve. Rarely, the infection resolves or is eradicated, but the headache may last longer than 3 months, which is termed persistent or chronic headache attributed to the infection (11).

Headache of variable duration caused by systemic infection, is reported without specific descriptive features and is usually accompanied by other symptoms and/or clinical signs of the infection as part of the 'infectious disease syndrome' that includes fever, chills, malaise, myalgia, arthralgia, and asthenia (118).

Box 40.20 describes the diagnostic criteria for headaches attributed to systemic infection based on the ICHD-3. These headaches must have an appropriate temporal association with the non-cephalic infection. Headaches associated with systemic infections have a varied presentation: (i) mild headache accompanied by malaise, fever, and other systemic infections, (ii) prominent headache, or (iii) headache due to intracranial infection like meningitis or encephalitis (119). According to ICHD-3, if a headache occurs with systemic infection in the presence of meningitis or encephalitis it is coded as a subtype of '9.1 Headache attributed to intracranial infection' (see also Chapter 41) (5).

Headaches attributed to systemic infection generally have non-specific characteristics and are often described as bilateral and diffuse, but occipital, fronto-temporal, or distinctive retro-ocular pain in certain cases can occur with variable intensity (118). Headaches related to infection can be throbbing or steady, and can be worsened by head movement or any Valsalva manoeuvre. The headaches may be associated with symptoms such as photophobia, phonophobia, conjunctival injection, neck guarding, nausea, and vomiting. The pain may be acute (< 3 months duration) or chronic/persistent (> 3 months' duration), occurring beyond the active infection. There are a number of studies, which reported that non-cephalitic infections can trigger or worsen primary headache disorders such as migraine, tension-type (120), and cluster headache (121) in susceptible individuals.

Box 40.19 Headache attributed to other disorder of homoeostasis

- **A** Any headache fulfilling criterion C.
- **B** A disorder of homoeostasis other than those described above, and known to be able to cause headache, has been diagnosed.
- **C** Evidence of causation demonstrated by at least one of the following:
  - **1** Headache has developed in temporal relation to the onset of the disorder of homoeostasis
  - **2** Headache has significantly worsened in parallel with worsening of the disorder of homoeostasis
  - **3** Headache has significantly improved or resolved in parallel with improvement in or resolution of the disorder of homoeostasis.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 40.20 Headache attributed to systemic infection

- **A** Headache of any duration fulfilling criterion C.
- **B** Both of the following:
  - **1** Systemic bacterial infection has been diagnosed
  - **2** No evidence of meningitic or meningoencephalitic involvement.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to onset of the systemic bacterial infection
  - **2** Headache has significantly worsened in parallel with worsening of the systemic bacterial infection
  - **3** Headache has significantly improved or resolved in parallel with improvement in or resolution of the systemic bacterial infection
  - **4** Headache has either or both of the following characteristics:
    - (a) Diffuse pain
    - (b) Moderate or severe intensity.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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When other neurological symptoms develop, direct involvement of cerebral structures (e.g. meningitis, encephalitis, brain abscess) should be suspected. In these cases, it is crucial to distinguish between headache attributed to a systemic infection and headache associated with intracranial infection. It is therefore necessary to do a cerebrospinal fluid examination to exclude intracranial infection in cases with high index of suspicion or particularly ill patients, particularly in the presence of neurological symptoms, including meningismus, focal neurological deficits, seizures, and altered level of consciousness (117).

Epidemiology

The incidence of headache associated with any one infectious disease is generally unpredictable with wide variation in reported rates. Little is known of the exact prevalence of this type of headache as the epidemiology of systemic infections that cause this type of headache vary widely, depending on the season, geographical location, and individual patterns of the disease. In addition, there is significant variability, as well in the propensity, of systemic infections to cause headache.

Aetiology

Headache is a common symptom in systemic infections, including bacterial infections ('9.2.1 Brucellosis, leptospirosis, rickettsia, legionella, and mycoplasma') or viral infections ('9.2.2 Influenza, adenovirus, dengue virus, West Nile virus) in the absence of meningitis or meningoencephalitis.

Headache may accompany sepsis as a part of septic encephalopathy (122). In bacterial infections due to *Rickettsiae, Ehrlichia canis*, Mediterranean spotted fever, Rocky Mountain spotted fever, and Q fever, headache occurs in a high percentage (up to 90%) of patients and closely parallels fever, with severe headache occurring with high temperature (123–125). In *Legionella pneumophila* and *Mycoplasma pneumoniae* infection, headache co-exists with fever, fatigue, arthralgia, myalgia, cough, and breathlessness (48,126). In leptospirosis, which also presents with severe kidney and liver disease, and occasionally meningeal involvement, headache occurs in 97% of cases (127). There are a number of diseases in which headache is less common than fever. In brucellosis, headache (128) is present in 23% of cases, much lower than the incidence of fever (91%) (129). Similarly, headache incidence is reported at < 10% in typhoid fever (130).

Systemic viral infections like influenza are accompanied by headache co-existing with fever, with an incidence ranging from 68% to 100% (131). A distinctive retro-orbital pain has been described in 26% of patients (132). In a case series of epidemic adenovirus infection, headache had an incidence of 83% with associated conjunctival injection of 51% (133). Retro-orbital pain, photophobia, nausea, abdominal pain, vomiting, skin rash, and severe headache (76–97%) have been reported in dengue fever (134–136). Among the viral illnesses, herpes simplex virus (HSV) and Epstein–Barr virus (EBV) seem particularly related to the occurrence of delayed or recurrent headaches. For example, chronic headache is the prominent symptom of HSV-induced chronic fatigue syndrome (137). Moreover, an increased frequency of EBV excretion has been found in patients with daily persistent headache (138) so that some authors recommended searching for EBV infection in patients with what new daily persistent headache (138).

Headaches attributed to infections may accompany a heterogeneous group of other systemic infections (9.2.3 in ICHD-3) frequently seen in immunosuppressed patients or in specific geographical areas, including systemic fungal infection, or infestation by protozoa or other parasites. The most common fungal infections associated with headache are due to pathogenic fungi like *Cryptococcus neoformans, Histoplasma capsulatum*, and *Coccidioides immitis*, as well as the opportunistic fungi like *Candida* species, *Aspergillus* species, and others. Among protozoa, infestations due to *Pneumocystis carinii* and *Toxoplasma gondii* were found to be associated with headache. Headache has also been reported with the nematode *Strongyloides stercoralis* (5). In the acute stage of malaria, fever has been found in 94% of patients and in 33.5% severe headache (139). During the acute stages of borreliosis, headache associated with erythema and fever has been reported in 88% of patients (140). Chronic headache (3 months) was found in 73–75% of patients with trypanosomiasis without any co-existing fever (141).

Pathophysiology

There is limited literature about the pathogenesis of headache due to systemic infection and the exact nature of these mechanisms remains unclear. However, several mechanisms causing headache associated with non-cephalic infection have been postulated, including direct (dependent on intrinsic characteristics of microorganisms) or indirect (depends on mechanisms induced by fever), or a combination of both.

In the direct mechanism, several cells are likely to be involved (activated microglia and monocytic macrophages, activated astrocytes, and blood–brain barrier and endothelial cells), as well as several immunoinflammatory mediators (cytokines, glutamate, COX-2/PGE-2 system, NO–inducible nitric oxide synthase system and reactive oxygen species system) (5,118). Some infective agents may invade brainstem nuclei such as locus coeruleus, trigeminal nuclei, and raphe nuclei to release substances that cause headache or endotoxins, which may activate inflammatory and nociceptive mediators (i.e. NO, prostaglandins, and cytokines), which play a role in generation of headache where the release of toxins or the toxic properties of cellular fragments activate headache mechanisms (142,143). Some studies reported that microorganism infected cells, particularly activated macrophages, release interleukin (IL), and interferon (IFN)-γ, which act as pyrogens, mediate inflammatory responses, and directly induce headache (118,144).

Indirect theory, however, postulates that the headache occurring due to systemic infection may be secondary to fever. In systemic infections, headache commonly co-exists with fever; however, headache can also occur in the absence of fever. Fever can be stimulated exogenously by pyrogens, such as inflammatory mediators and toxins, or directly, by microorganisms or fragments of microorganisms. Endogenous pyrogens release additional pyrogens from stimulated leukocytes or induce IL-1 and IFN-γ, which also induce headache. Pyrogens also induce increased arachidonic acid metabolites such as the COX-derived prostaglandins, prostacyclin, and thromboxane. PGE-2 has vasoactive properties and could be indirectly implicated in any vascular component of headache (145). Headache can be secondary to either increase or decrease in cerebral blood flow, most commonly the former

produced by high pCO_2. Hypotension due to shock can induce a decrease in cerebral blood flow and sometimes account for headache (118). However, the great variability in their propensity for causing headache indicates that systemic infections do not have this effect simply through fever and exogenous or endogenous pyrogens, which indicates that under different circumstances the pain may have different mechanisms (5).

Treatment

Management of this type of headache includes specific treatment directed to the underlying infection (if possible). Other recommendations include treatment of fever with antipyretics and treatment of associated inflammation with NSAIDs. Headache-specific therapy is also recommended for those patients who are predisposed to primary headache disorders and who develop systemic infection-induced migraine or cluster headaches (117).

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41

Headache associated with intracranial infection

Matthijs C. Brouwer and Jonathan P. Gladstone

Introduction

Headache is a common presenting symptom in patients with intracranial infections and may be the only symptom (1–3). A wide range of neurological infections, both acute and chronic, can be included in the differential diagnosis of headache, although only a minority of headache patients will eventually be diagnosed with a neurological infection (4). In patients that have experienced an intracranial infection, persisting headache occurs, although the incidence of headache in these patients may not exceed that of the general population (5,6). Within the International Classification of Headache Disorders, third edition (2018; ICHD-3), headache due to intracranial infections is described in Part 2 (Secondary Headaches), Chapter 9.1 (7). In the classification, a distinction is made between acute, chronic, and persisting headache associated with intracranial infections (7). In clinical practice, when patients suspected of having an acute intracranial infection present, the focus of attention will be on diagnosing the neurological infection and subsequent treatment (8). This also holds true for patients with chronic meningitis, which often poses a diagnostic challenge and not only includes infection due to viruses, bacteria, fungi, yeast, and parasites, but also autoimmune and inflammatory conditions such as sarcoidosis (9). Classification and treatment of headache in these patients will often not be the primary concern of the physician. In contrast, in patients with persisting headache following intracranial infection the differential diagnosis may include other headache syndromes, such as migraine or tension-type headache (5). In this chapter we will discuss the epidemiology, diagnosis, and treatment of headache associated with intracranial infections.

Bacterial meningitis

Epidemiology

The incidence of acute bacterial meningitis is 1.4–2.6 per 100,000 persons per year in high-income countries, and may be 100-fold higher in poor-resource settings with high rates of human immunodeficiency virus (HIV) infection and meningitis epidemics (10–12). The epidemiology of bacterial meningitis varies with geographical region, age, HIV infection rate, and other causes of immunosuppression, and with the availability of vaccines (13).

The introduction of conjugate vaccines against *Haemophilus influenzae* type B, *Streptococcus pneumoniae* and *Neisseria meningitidis* has changed the epidemiology of bacterial meningitis over the past two decades (13). The first widely used conjugate vaccine against *H. influenzae* type b (Hib) has led to a virtual elimination of Hib meningitis in higher-income countries (11,13). Currently, the Hib vaccine had been introduced in 184 countries, but only reaches 50% of children worldwide (14). The introduction of conjugate vaccines against seven serotypes of *S. pneumoniae* that are among the most prevalent in children aged 6 months–2 years has reduced the rate of invasive pneumococcal infections in young children and in older persons by 25% (13,15). However, a 61% increase in pneumococcal serotypes not included in this vaccine was shown, suggesting serotype replacement and emphasizing the need for continuing surveillance and the development of new vaccines with wider coverage (10). In recent years, 10- and 13-valent pneumococcal vaccines have been introduced, providing higher coverage (13,16). The incidence of meningococcal meningitis varies over time, per serogroup and geographical location, even in the absence of vaccination programmes (13). Major epidemics of meningococcal meningitis with incidence rates of 1% of the population occurred in the so-called 'meningitis belt', a region of sub-Saharan African countries (17,18). Serogroups B, C, and Y predominantly cause sporadic meningitis in high-income countries (19,20). Introduction of the conjugate meningococcal group C vaccine has led to a decrease in meningococcal meningitis serogroup C incidence by more than 90% (13). Owing to the implementation of these vaccine strategies, the incidence of bacterial meningitis in children has sharply decreased, and bacterial meningitis has become a disease primarily occurring in adults, caused by *S. pneumoniae* and *N. meningitidis* in 85% of cases (1,21). Less common causes of bacterial meningitis such as *Listeria monocytogenes* or *Staphylococcus aureus* are often related to specific comorbid conditions, such as cancer, immunocompromised state, old age, or endocarditis (Table 41.1) (22,23).

Table 41.1 Causative microorganisms of adult bacterial meningitis and clinical characteristics.

Microorganism	Frequency (%)	Mean age (years)	Risk factors	Headache on presentation (%)	Mortality (%)
Streptococcus pneumoniae (50)	70	59	Otitis, sinusitis, pneumonia	85	20
Neisseria meningitides (19)	15	38	–	91	4
Listeria monocytogenes (23)	5	69	Age > 50 years, cancer, immunocompromised	80	36
Haemophilus influenza (70)	4	47	Otitis	100	6
Staphylococcus aureus (22,71)	3	57	Endocarditis, pneumonia	75	67

Clinical characteristics and headache prevalence

The classic symptoms and signs of bacterial meningitis are neck stiffness, fever, and impaired consciousness (1). The presence of this classic triad is, however, low and identified in less than half of children and adults with proven bacterial meningitis (1,24). Headache is a common symptom of bacterial meningitis, which is found in approximately 90% of adults and 75% of children over 5 years of age with bacterial meningitis (1,24). In a retrospective study analysing the sequence and development of signs and symptoms before hospital admission in meningococcal disease in 448 children and adolescents, it was found that headache was the initial symptom in 94% of patients over 5 years of age old (25). In this study, characteristic symptoms of meningococcal meningitis of rash, neck stiffness, and impaired consciousness did not develop until late in the prehospital illness. Owing to the low specificity of headache for the diagnosis of bacterial meningitis, it is, however, of little use in the diagnostic work-up. When headache was added to the classic triad of symptoms, 95% of patient had a least two out of four symptoms of headache, neck stiffness, fever, and an altered mental status (1). The specificity of these findings is probably also low, and especially in childhood bacterial meningitis and in elderly patients the typical findings on the clinical history and physical examination may be absent (26). Studies have been performed to assess whether a sudden increase in headache provoked by horizontal rotation of the head 2–3 times per second, described as 'jolt accentuation', could be used detect cerebrospinal fluid (CSF) pleocytosis (27). Although the initial study showed a high sensitivity, subsequent studies showed that the test performed very poorly (28,29). Other symptoms and clinical tests, such as neck stiffness, and Kernig and Brudzinski signs also have poor diagnostic accuracy (8). Therefore, in patients with suspected bacterial meningitis, a lumbar puncture should always be performed to confirm or rule out the diagnosis.

Headache characteristics

In patients with bacterial meningitis headache may have a sudden onset (30), but in most patients it develops gradually and may initially be localized at a co-existing ear or sinus infection. Because of the sudden onset in some patients, the patient may initially be suspected as having a subarachnoid haemorrhage (SAH), especially if fever is absent (30). Initial cranial imaging in bacterial meningitis may also put the physician on the wrong track, as pus in the CSF may show up as a so-called 'pseudo-SAH' on CT (Figure 41.1) (31,32).

Qualitative studies have not been performed that address characteristics of headache in patients with bacterial meningitis

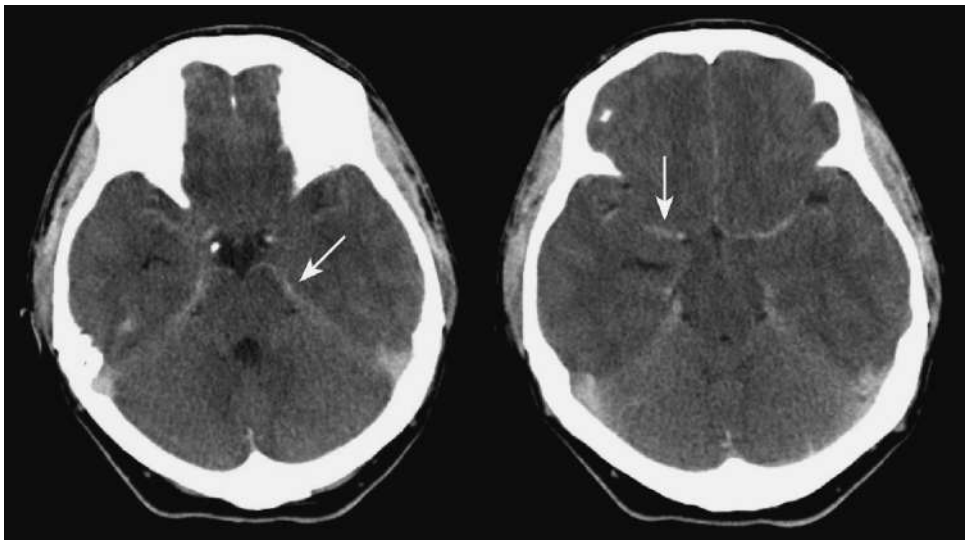

Figure 41.1 Cranial computed tomography showing a hyperdense aspect of the subarachnoid space caused by a high protein and leukocyte content of the cerebrospinal fluid, mimicking the radiological image of a subarachnoid haemorrhage (SAH), which is referred to pseudo-SAH.

Box 41.1 Diagnostic criteria for headache attributed to bacterial meningitis or meningoencephalitis

- **A** Headache of any duration fulfilling criterion C.
- **B** Bacterial meningitis or meningoencephalitis has been diagnosed.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of the bacterial meningitis or meningoencephalitis
  - **2** Headache has significantly worsened in parallel with worsening of the bacterial meningitis or meningoencephalitis
  - **3** Headache has significantly improved in parallel with improvement in the bacterial meningitis or meningoencephalitis
  - **4** Headache is either or both of the following:
    - (a) Holocranial
    - (b) Located in the nuchal area and associated with neck stiffness.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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during the acute phase. The characteristics attributed to headache in bacterial meningitis are that it is generalized, severe, and unremitting (33). Following the diagnostic criteria for headache attributed to bacterial meningitis according to the ICHD-3 (Box 41.1), the diagnosis of headache in bacterial meningitis can be made when there is a diagnosis of bacterial meningitis and a clear temporal relationship between development and resolution of bacterial meningitis and headache (7). Furthermore, the headache should be generalized or located in the neck and associated with neck stiffness. In general, these criteria are not likely to be used to establish the diagnosis of headache in patients with bacterial meningitis, given the obviousness of the diagnosis of headache in bacterial meningitis patients. Furthermore, the criteria only facilitate a retrospective diagnosis as a temporal relation must be present when the diagnosis is made (Box 41.1). It is unclear why the holocranial or nuchal area location of the headache (Box 41.1) is included as a criterion, given the lack of studies on headache quality in patients with bacterial meningitis.

Several factors can contribute to the development of headache in patients with bacterial meningitis. Firstly, the majority of patients with bacterial meningitis have an elevated intracranial pressure. In a large prospective cohort study the mean intracranial pressure in patients with bacterial meningitis was 370 mm H_2O (normal upper limit 200 mm) (1). Controversies exist about the clinical efficacy of lowering intracranial pressure, either by placement of CSF catheters, or the use of osmotherapy by means of glycerol or mannitol (34–37). So far, no clear benefit has been shown on mortality or the development of neurological sequelae (37). In these studies, duration or severity of headache has not been evaluated as outcome parameter. A second cause of headache in patients with bacterial meningitis may be the direct stimulation of meningeal nociceptors by bacterial products, mediators of inflammation, and reactive oxygen species (33). Furthermore, a range of complications of bacterial meningitis may cause or aggravate headache, including hydrocephalus, subdural empyema, cerebral abscess, cerebral infarctions, and cerebral haemorrhages, which have been described to occur in 2–25% of patients (38–42). Some of these complications require urgent neurosurgical intervention and therefore a sudden increase in headache during treatment for bacterial meningitis should prompt cranial imaging to detect these conditions.

Diagnosis and treatment

Rapid diagnosis and treatment of bacterial meningitis reduces mortality and neurological sequelae (8). When bacterial meningitis is suspected, CSF examination is of the utmost importance to confirm the diagnosis and rationalize antibiotic treatment. In selected patients with risk factors for space-occupying lesions cranial imaging is indicated before the lumbar puncture is performed to assess whether this can be done safely (8,43). Cranial imaging, however, has been identified as an import source of delay in administration of antibiotics, resulting in increased mortality and morbidity (44,45). Therefore, treatment with antibiotics and adjunctive dexamethasone should be initiated before the patients goes to the scanner when cranial imaging is indicated. Characteristic CSF findings in acute community-acquired bacterial meningitis are polymorphonuclear pleocytosis, hypoglycorrhachia, and raised CSF protein concentrations (1). CSF culture is the gold standard for diagnosis of bacterial meningitis and is positive in 80–90% of cases before treatment has started (8). Polymerase chain reaction (PCR) may be useful to identify the causative bacteria in culture negative cases, especially in patients that received antibiotic treatment before the lumbar puncture was performed (8,11).

Empirical antimicrobial treatment for bacterial meningitis depends on local epidemiology, patient's age, and resistance rates (46). If resistance rates are low, a third-generation cephalosporin combined with amoxicillin/ampicillin suffices, otherwise vancomycin has to be added to this regimen (46). Adjunctive dexamethasone was shown to be beneficial in children and adults in high-income countries in the most recent Cochrane systematic review and meta-analysis including 25 trials involving 4121 participants (47). Therefore, adjunctive dexamethasone is currently advised in all adults and children with suspected bacterial meningitis in high-income countries. In resource-poor settings no benefit of dexamethasone was observed (47). Other adjunctive treatments such as therapeutic hypothermia, acetaminophen, and glycerol have been tested in randomized clinical trials but either showed no effect (acetaminophen) or caused excess mortality (hypothermia, glycerol) (48,49).

Specific treatment of headache in patients with bacterial meningitis has not been studied. In general, treatment with analgesics and antipyretics will be started upon admission to relieve headache symptoms.

Outcome and postbacterial meningitis headache

Individual predictors of outcome in patients with bacterial meningitis are the patient's age, level of consciousness on admission, the causative microorganism, CSF white blood cell count, and signs of septic shock (1). Mortality rates vary per causative microorganism and are approximately 20% in pneumococcal meningitis, 5% in meningococcal meningitis, and 35% in *L. monocytogenes* meningitis (19,23,50). Up to half of patients experience neurological sequelae, especially in pneumococcal meningitis, which may consist of focal neurological abnormalities, neuropsychological defects, and hearing loss (1,51,52).

Box 41.2 Diagnostic criteria for chronic headache attributed to bacterial meningitis or meningoencephalitis

- **A** Headache fulfilling criteria for '9.1.1 Headache attributed to bacterial meningitis or meningoencephalitis', and criterion C below.
- **B** Bacterial meningitis or meningoencephalitis remains active or has resolved within the last 3 months.
- **C** Headache has been present for > 3 months.

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Headache after bacterial meningitis is classified by the ICHD-3 in two separate categories, which differ in whether the bacterial meningitis needs to be resolved or do not fulfil the criteria (**Boxes 41.2 and 41.3**) (7).

The frequency of headache after experiencing bacterial meningitis has been studied in one retrospective and one longitudinal study (5,6). In the retrospective study, 70 of 141 (50%) identified patients (17 bacterial meningitis, 53 viral meningitis) filled out questionnaires concerning headache following the disease episode (5). Controls were hospital visitors without neurological disease. The frequency of headache in this population was 26% prior to meningitis and 43% after meningitis versus 28% in the control group. However, the retrospective design, choice of controls, and probable selection bias limit the interpretation of these results. The second study presented incidence data from the Nord-Trøndelag Health Survey (HUNT 3), a large, longitudinal, population-based study on headache incidence (6). In this study 43 patients with prior intracranial infections, mostly bacterial and viral meningitis, were interviewed an average of 11.2 years after the infection. Any type of headache was present in 18 of 43 patients (42%) versus 14,202 of 39,647 (36%) controls, which was not significantly different (odds ratio 1.10, 95% confidence interval 0.58–2.07) (6). When specified for migraine or tension-type headache, no difference was identified. Interestingly, the frequency of headache in this population was similar to that in the retrospective study. Treatment of persistent or chronic headache following bacterial meningitis has not been studied, but it is reasonable to base the treatment on headache characteristics: if the headache has a tension-type headache quality, it should be treated accordingly.

Viral meningitis

Viruses are thought to be the major cause of the aseptic meningitis syndrome, a term that is used to define any meningitis for which a cause is not apparent after initial evaluation. Aseptic meningitis is been characterized as a self-limiting disease with flu-like symptoms, including headache, fever, and general malaise. The majority of patients (70%) presenting with a CSF pleocytosis (> 5 cells/mm^3) were eventually diagnosed as having aseptic meningitis, and in only a small proportion of these patients was a virus detected (4). Enteroviruses are the most commonly identified cause of viral meningitis, found in 3% of this population.

The diagnosis of viral meningitis is made in the presence of CSF pleocytosis, with no indication of bacterial, mycobacterial, fungal, or other specific cause of meningitis. Several clinical prediction rules have been designed to rule out bacterial meningitis by use of clinical characteristics, serum markers of inflammation (C-reactive protein and procalcitonin), and CSF parameters of inflammation (4,8). Although most of these rules have good test characteristics, they are often not validated in independent cohorts and include low numbers of patients with bacterial meningitis, limiting the clinical usefulness. Therefore, most of the patients who eventually are diagnosed with viral meningitis will be admitted for observation until clinical recovery has set in and CSF cultures are negative (8). An important differential diagnosis in patients with viral meningitis and headache is the syndrome of transient headache and neurological deficits with CSF lymphocytosis (HaNDL—see also Chapter 44). Both are diagnoses of exclusion and will present with lymphocytic meningitis (53). As HaNDL may also be accompanied by fever, the distinction may be impossible.

No studies have been performed that assess the quality of headache in viral meningitis, but, in general, it is considered to be similar to that in bacterial meningitis (54). ICHD-3 criteria for diagnosing headache in patients with viral meningitis are similar to those in bacterial meningitis and the diagnosis requires a clear temporal relationship between established viral meningitis and headache, which should be holocranial or located in the nuchal area and associated with neck stiffness (**Box 41.4**) (7).

To specifically allocate the headache to viral meningitis neuroimaging is required to show enhancement of leptomeninges (**Box 41.5**) (7). In clinical practice, the diagnosis of viral meningitis is not based on neuroimaging and leptomeningeal enhancement may be absent.

Box 41.3 Diagnostic criteria for persistent headache attributed to past bacterial meningitis or meningoencephalitis

- **A** Headache fulfilling criteria for '9.1.1 Headache attributed to bacterial meningitis or meningoencephalitis', and criterion C below.
- **B** Bacterial meningitis or meningoencephalitis has resolved.
- **C** Headache has persisted for > 3 months after resolution of the bacterial meningitis or meningoencephalitis.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 41.4 Diagnostic criteria for headache attributed to viral meningitis or encephalitis

- **A** Any headache fulfilling criterion C.
- **B** Viral meningitis or encephalitis has been diagnosed.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of the viral meningitis or encephalitis
  - **2** Headache has significantly worsened in parallel with worsening of the viral meningitis or encephalitis
  - **3** Headache has significantly improved in parallel with improvement in the viral meningitis or encephalitis
  - **4** Headache is either or both of the following:
    - (a) Holocranial
    - (b) Located in the nuchal area and associated with neck stiffness.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 41.5 Diagnostic criteria for headache attributed to viral meningitis

A Headache fulfilling criteria for '9.1.2 Headache' attributed to viral meningitis or encephalitis'.
B Neuroimaging shows enhancement of the leptomeninges exclusively.

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Treatment of headache attributed to viral meningitis is symptomatic with analgesics and antipyretics, and symptoms are expected to wane in a matter of days. Chronic and residual headache due to viral meningitis has not been systematically described, but is not expected to be above that of the normal population.

Viral encephalitis

In contrast to viral meningitis, viral encephalitis is a severe infection with high mortality (2,55). Key symptoms of viral encephalitis are fever, headache, and altered mental status. Furthermore, seizures and focal neurological deficits are commonly present. Headache has been reported on admission in 50–75% of patients with viral meningitis (2), but the quality and severity of the headache has not been studied. In patients with suspected viral encephalitis, the differential diagnosis is often broad, including other infectious diseases such as tuberculous meningitis or bacterial meningitis, and several autoimmune diseases (e.g. acute disseminated encephalomyelitis, paraneoplastic meningitis) (2,55). The most common causes of viral encephalitis include herpes simplex virus, Japanese encephalitis virus, varicella zoster virus, tick-borne encephalitis virus, and West Nile virus, although the epidemiology is highly variable, depending on the region. Diagnostic work-up for patients with suspected meningitis include cranial magnetic resonance imaging (MRI), CSF examination, including PCR for neurotropic viruses, and sometimes electroencephalography (56). Whenever viral encephalitis is suspected, immediate treatment with antiviral therapy is warranted (Box 41.6).

Cerebral abscess

Brain abscess is a focal intracerebral infection consisting of an encapsulated collection of pus cause by bacteria, mycobacteria, fungi, protozoa, or helminths (57,58). The incidence of bacterial brain abscess is 0.4–0.9 per 100,000 per year, and is thought to be considerably higher in patients with specific risk factors, such as HIV infection, or recipients of a solid organ transplant (59–61). A meta-analysis of clinical characteristics, treatment, and outcomes of brain abscess patients, including 9699 patients from 123 studies, showed that the most common presenting symptom was headache, which was present in 69% of patients (62). Headache in patients with brain abscess is thought to be caused by the raised intracranial pressure, which is accompanied by nausea and/or vomiting in 47% of cases and 35% of patients have papilloedema (62). Nausea and/or vomiting are also included as a criterion contributing to the ICHD-3 diagnosis of headache attributed to cerebral abscesses (Box 41.7). Furthermore, a temporal relationship between the documented abscess and the headache is an important criterion for the diagnosis. Headache may suddenly worsen in patients with rupture of the abscess into a ventricle, leading to ventriculitis and acute hydrocephalus (62). This requires immediate cranial imaging and often necessitates placement of an external CSF catheter to treat the hydrocephalus and, when indicated, facilitate intraventricular antibiotic treatment (63).

In patients with cerebral abscess it is important to identify and treat any underlying focus of infectious, which is continuous with the abscess in ~50% of patients (e.g. sinus, mastoid, trauma, neurosurgery) and haematogenous in 35% (heart, lung) (62). Identification of a primary focus of infection may also reveal the causative bacterium. However, in a substantial number of patients with brain abscess, abscess aspiration is required to acquire the pathogen, and will simultaneously reduce the size of the abscess (62). Treatment consists of intravenous antibiotic therapy for 6 weeks or more, depending on clinical condition of the patients and radiological characteristics of the abscess.

Box 41.6 Diagnostic criteria for headache attributed to viral encephalitis

A Headache fulfilling criteria for '9.1.2 Headache attributed to viral meningitis or encephalitis'.
B Either or both of the following:
1 Neuroimaging shows diffuse or multifocal brain oedema
2 At least one of the following:
(a) Altered mental status
(b) Focal neurological deficits
(c) Seizures.

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Box 41.7 Headache attributed to localized brain infection

A Any headache fulfilling criterion C.
B A localized brain infection has been demonstrated by neuroimaging and/or specimen analysis.
C Evidence of causation demonstrated by at least two of the following:
1 Headache has developed in temporal relation to development of the localized brain infection, or led to its discovery
2 Headache has significantly worsened in parallel with deterioration of the localized brain infection shown by either of the following:
(a) Worsening of other symptoms and/or clinical signs arising from the localized brain infection
(b) Evidence of enlargement (or rupture, in the case of brain abscess) of the localized brain infection
3 Headache has significantly improved in parallel with improvement in the localized brain infection
4 Headache has at least one of the following characteristics:
(a) Intensity increasing gradually, over several hours or days, to moderate or severe
(b) Aggravated by straining or other Valsalva manoeuvre
(c) Accompanied by fever, nausea, and/or vomiting
(d) Unilateral, and ipsilateral to the localized brain infection.
D Not better accounted for by another ICHD-3 diagnosis.

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Subdural empyema

Subdural empyema is a collection of pus in the subarachnoidal space (between the dura mater and arachnoidea), which is often associated with ear, mastoid, or sinus infection (39,64). Clinical characteristics consist of headache, fever, and altered mental status (64). It is important to realize that cerebral venous thrombosis may co-exist in patients with mastoiditis and empyema, and provide an alternate explanation for the headache.

Headache attributed to subdural empyema has similar ICHD-3 criteria as headache in patients with brain abscess consisting of a diagnosis of subdural empyema, and evidence of a causal relation between the development of the empyema and the headache. Treatment of subdural empyema consists of antibiotic therapy for 6 weeks or more and neurosurgical removal of the empyema depending on the size of the empyema, clinical condition of the patient, and degree of midline shift.

Tuberculous meningitis

Meningitis due to tuberculosis is an important problem worldwide, with the heaviest burden of disease in Africa and South East Asia. Between 50% and 80% of patients have headache on presentation, with fever, anorexia, and vomiting being the other key clinical characteristics (65). The headache is caused by a combination of factors: patients not only often have raised intracranial pressure, but also the inflammatory response leading to meningeal irritation contributes to the headache. Complications of tuberculous meningitis consist of hydrocephalus, cerebral infarctions, and cerebral tuberculomas, which can all result in headache. A definite diagnosis of tuberculous meningitis is made by positive CSF Ziehl–Neelsen staining, *Mycobacterium tuberculosis* PCR, or culture, while a probable diagnosis can be made based on the pattern of CSF abnormalities in combination with pulmonary or extrapulmonary tuberculosis (66). Treatment consists of a combination of antituberculosis drugs and dexamethasone, and must be continued for at least 6 months. Despite adequate treatment, mortality is still high (~50%) (67).

Headache in HIV-positive patients

Headache is a common symptom in HIV-positive patients (33,70). A 2012 cross-sectional study from the USA showed that 107 of 200 HIV-positive patients (54%) experienced headache, of which most met the ICHD-2 criteria for migraine (n = 88; 85%) and tension-type headache (n = 15; 15%) (68). Only a minority (n = 4; 2%) had secondary headache. In this study and others the prevalence of headache was proportional to the degree of immunocompromise (33,68). Newly developed headache related to the HIV infection can be caused by the primary HIV infection, or can be secondary to opportunistic infection. Headache in patients with a recent HIV seroconversion can be due to HIV meningitis, which occurs in 1–2% of patients (33). The most common secondary causes of headache in HIV-positive patients are cerebral toxoplasmosis, cryptococcal meningitis, central nervous system lymphoma, tuberculous meningitis, and progressive multifocal encephalopathy. In most of these disorders headache is one of the symptoms, and focal neurological deficits, cognitive slowing, or altered mental status will also occur. The exception to this is cryptococcal meningitis, in which headache is a prominent symptom, present in 99% of patients, and can be accompanied by vomiting, papilloedema and loss of vision (69). The ICHD-3 criteria for headache in cryptococcal meningitis and meningitis due to other fungi and parasites are presented in **Box 41.8**.

Box 41.8 Headache attributed to intracranial fungal or other parasitic infection

- **A** Any headache fulfilling criterion C.
- **B** Intracranial fungal or other parasitic infection has been diagnosed.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset the intracranial fungal or other parasitic infection
  - **2** Headache has significantly worsened in parallel with worsening of the intracranial fungal or other parasitic infection
  - **3** Headache has significantly improved in parallel with improvement in the intracranial fungal or other parasitic infection
  - **4** Headache develops progressively, and is either or both of the following:
    - (a) Holocranial
    - (b) Located in the nuchal area and associated with neck stiffness.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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There is considerable variability in the location, quality, severity, and presence of associated symptoms in headache attributable to primary HIV-1 infection and headaches secondary to opportunistic infections, making the diagnosis of headache in HIV-infected patients difficult (33). The work-up for HIV-positive patients with headache depends on their immune status: if the CD4 count is > 200 cells/μl, the patient can be considered to have a low risk for opportunistic infections and primary headache may be the more likely diagnosis. In patients with a low CD4 count, a cranial MRI is indicated to identify opportunistic infections, followed by CSF examination when no abnormalities are shown on MRI.

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42

Remote causes of ocular pain

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Introduction

Ocular and periocular pain may occur with processes originating remotely from the eye, including primary headache disorders, pain originating in branches of the trigeminal nerve, and, occasionally, disorders of the upper cervical spine. The primary headaches producing periocular pain include migraine, tension-type headache, cluster headache and other trigeminal autonomic cephalgias, paroxysmal hemicrania, and other miscellaneous headaches not associated with a structural lesion. This chapter focuses on unusual primary headache disorders that manifest as eye pain, as well as secondary causes of ocular pain, including ophthalmic and orbital conditions, inflammatory and infectious processes, cranial neuralgias, and vascular disorders.

Primary headache disorders manifesting as eye pain

Primary stabbing headache

Previously known as ice pick headache, jabs and jolts syndrome, ophthalmodynia periodica, and idiopathic stabbing headache, primary stabbing headache commonly affects the ocular area and produces a sense of fear in its sufferers (Box 42.1) (see also Chapter 23). There are sudden, unprovoked paroxysms of severe pain that occur as a stab or series of stabs. Many patients have other co-existing primary headache disorders. The ophthalmic division of the trigeminal nerve is most frequently affected, followed by the face or other regions of the head; the site of pain varies in individual patients, who may experience up to 50 attacks daily. There are no autonomic or other accompanying features.

Laboratory testing

A secondary cause is uncommon, especially if the pain migrates. Giant cell arteritis (GCA) is a consideration in older adults. Imaging may be considered if the pain does not improve with treatment.

Treatment

Indomethacin is usually effective for preventing attacks. Melatonin, gabapentin, and amitriptyline may also be helpful.

Hemicrania continua

Hemicrania continua (HC) is uncommon and the diagnosis is frequently missed, particularly if the pain is periocular (see also Chapter 21). The pain is strictly unilateral, located in the orbital or retro-orbital area in 77–83% of patients (1). Rare cases of bilateral pain have been reported. The pain may be throbbing, non-throbbing, or a combination of both. It is constantly present, with punctuated exacerbations lasting 5–60 minutes, and associated with the autonomic symptoms seen in HC, most frequently tearing and conjunctival injection (1). Migrainous features, such as nausea, vomiting, photophobia, and phonophobia may also be present during exacerbations. Aura is rare.

Laboratory testing

In addition to neuroimaging to exclude a secondary cause, evaluations for GCA may be warranted in patients over 60 years of age, particularly if other manifestations of GCA are seen in the patient's history. Responsiveness to indomethacin (150 mg daily or more, if tolerated) is required for the diagnosis.

Treatment

If indomethacin is not tolerated, topiramate, *Boswellia* (a genus of trees), greater occipital nerve blocks, and occipital nerve stimulation may be helpful (2).

Migraine 'variants': benign episodic pupillary mydriasis

A separate entity, benign episodic pupillary mydriasis, produces anisocoria that may be associated with blurred vision, head pain, photophobia, conjunctival injection or transient visual obscurations (3). The attacks last from minutes to a week, with a median duration of 12 hours. The anisocoria is generally ≤ 3 mm, and the pupil may or may not react to light. The mechanism is uncertain, but most reported patients are women with a history of migraine. Physiological anisocoria and benign episodic pupillary mydriasis may co-exist in the same patient.

Diagnostic testing

Unilateral mydriasis is very uncommonly a manifestation of an aneurysm and appropriate imaging studies may be warranted for the first event.

Box 42.1 Other primary headache disorders causing ocular or periocular pain

Primary stabbing headache

A Head pain occurring spontaneously as a single stab or series of stabs and fulfilling criteria B–D.
B Each stab lasts for up to a few seconds.
C Stabs recur with irregular frequency, from one to many per day.
D No cranial autonomic symptoms.
E Not better accounted for by another ICHD-3 disorder.

Hemicrania continua

A Unilateral headache fulfilling criteria B–D.
B Present for > 3 months, with exacerbations or moderate or greater intensity.
C Either or both of the following:
  1 At least one of the following symptoms or signs, ipsilateral to the headache:
    (a) Conjunctival injection and/or lacrimation
    (b) Nasal congestion and/or rhinorrhoea
    (c) Eyelid oedema
    (d) Forehead and facial sweating
    (e) Forehead and facial flushing
    (f) Sensation of fullness in the ear
    (g) Miosis and/or ptosis
  2 A sense of restlessness or agitation, or aggravation of the pain by movement.
D Responds absolutely to a therapeutic dose of indomethacin (150–225 mg PO daily in adults).
E Not better accounted for by another ICHD-3 diagnosis.

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Treatment

Benign episodic pupillary mydriasis resolves spontaneously. Associated headaches are treated with migraine symptomatic therapies.

Secondary headache disorders producing ocular and periocular pain

Recurrent painful ophthalmoplegic neuropathy

Cranial nerve palsies are reported in migraine, although the syndrome known as 'ophthalmoplegic migraine' is no longer considered a type of migraine by the International Classification of Headache Disorders (ICHD) (Box 42.2). It is now termed 'recurrent painful ophthalmoplegic neuropathy' (RPON) and classified as a painful neuropathy rather than a migraine subtype (4). The aetiology and classification of the syndrome remain controversial. The source of debate in classification arises because some patients have recurrent attacks with no identifiable structural abnormality, a phenotype suggesting a true migraine variant that recurs and resolves without corticosteroid treatment. Others have a structural cause or episodes that resolve only with corticosteroid treatment, suggesting that the primary process is not migraine (5).

The syndrome was originally described in children with episodes of headache followed by an ocular motor palsy, often lasting weeks after resolution of the headache. The oculomotor nerve is most commonly involved, although trochlear and abducens paresis may occur. The diagnostic criteria for RPON specify at least two attacks of a migraine-like headache accompanied or followed within 4 hours by paresis of one or more of the ocular motor nerves (III, IV, VI). Parasellar, orbital fissure, or posterior fossa pathology must be excluded. The headache is usually ipsilateral to the ocular motor cranial neuropathy, and may persist for a week or more. The ipsilateral pupil is commonly dilated in cases of oculomotor RPON.

Ophthalmoplegia may be permanent and is rarely accompanied by aberrant regeneration. The condition is rare, with an estimated incidence of 0.7 per 1,000,000 (6). Neuroimaging studies (magnetic resonance imaging (MRI) with gadolinium) frequently demonstrate thickening and enhancement of the oculomotor nerve fascicle, suggesting an inflammatory process (6). The enhancement may persist for months to years. Acute treatment with corticosteroids provides prompt resolution of headaches and may prevent a permanent neurological deficit. The pathophysiology of RPON is uncertain. Trigeminovascular activation with sterile inflammation and demyelination of the oculomotor nerve at its entry from the brainstem is postulated. Other secondary causes of the RPON syndrome include an oculomotor nerve schwannoma, midbrain vascular anomaly, and carotid stenosis.

Laboratory testing

Neuroimaging in RPON rarely demonstrates a secondary cause in patients with a typical history of recurrent episodes and a normal neurological examination. Patients with new-onset headaches, headaches with a progressive course, headaches with a significant change in pattern, headaches that never alternate sides, and headaches associated with ophthalmoparesis, any other neurological findings, or seizures have a substantially higher likelihood of a secondary cause such as tumour, arteriovenous malformation, or other structural lesion (7).

Treatment

RPON is generally treated with prednisone, which relieves the pain and may hasten recovery of the cranial mononeuropathy.

Trigeminal neuralgia and herpes zoster-related neuralgia

The most common of the cranial neuralgias, trigeminal neuralgia (TN) is one of the most painful conditions affecting humans (see also Chapter 27). It may begin at any age, with 90% of patients over the age of 40 years (peak age 50–60 years) (8). Multiple sclerosis (MS) should be considered in patients under 50 years of age. The pain is in the maxillary and mandibular divisions of the face, with only 5% of cases involving the ophthalmic nerve. Thus, TN is an uncommon cause of periorbital or ocular pain. Typical TN produces sharp, sudden, stabbing pain lasting less than a second to a few seconds, sometimes with clusters lasting up to 2 minutes (Box 42.2). Patients often wince coincident with the excruciating pain, hence the term *tic douloureux* (painful spasm). There is usually a brief refractory period and most patients identify triggers, such as tactile stimuli, eating, jaw, or tongue movement, or a thermal stimulus.

Box 42.2 Secondary headache disorders causing ocular or periocular pain

Recurrent painful ophthalmoplegic neuropathy

A At least two attacks fulfilling criterion B.
B Unilateral headache accompanied by ipsilateral paresis of one, two, or all three ocular motor nerves.
C Orbital, parasellar, or posterior fossa lesion has been excluded by appropriate investigation.
D Not better accounted for by another ICHD-3 diagnosis.

Classical trigeminal neuralgia

A At least three attacks of unilateral facial pain fulfilling criteria B and C.
B Occurring in one or more divisions of the trigeminal nerve, with no radiation beyond the trigeminal distribution.
C Pain has at least three of the following four characteristics:
  1 Recurring in paroxysmal attacks lasting from a fraction of a second to 2 minutes
  2 Severe intensity
  3 Electric shock-like, shooting, stabbing, or sharp in quality
  4 Precipitated by innocuous stimuli to the affected side of the face.
D No clinically evident neurological deficit.
E Not better accounted for by another ICHD-3 disorder.

Painful trigeminal neuropathy attributed to acute herpes zoster

A Unilateral continuous or near-continuous pain in the distribution of nervus intermedius and fulfilling criterion C.
B One or more of the following:
  1 Herpetic eruption has occurred in the territory of nervus intermedius
  2 Varicella zoster virus (VZV) has been detected in cerebrospinal fluid by polymerase chain reaction (PCR).
  3 Direct immunofluorescence assay for VZV antigen or PCR assay for VZV DNA is positive in cells obtained from the base of the lesions.
C Pain developed in temporal relationship to the herpes zoster.
D Not better accounted for by another ICHD-3 disorder.

Postherpetic trigeminal neuropathy

A Unilateral head and/or facial pain persisting or recurring for ≥ 3 months and fulfilling criterion C.
B History of acute herpes zoster affecting a trigeminal nerve branch or branches.
C Evidence of causation demonstrated by both of the following:
  1 Pain developed in temporal relationship to the acute herpes zoster
  2 Pain is located in the distribution of the same trigeminal branch or branches.
D Not better accounted for by another ICHD-3 disorder.

Cervicogenic headache

A Any headache fulfilling criterion C.
B Clinical, laboratory, and/or imaging evidence of a disorder or lesion within the cervical spine or soft tissues of the neck, known to be able to cause headache.
C Evidence of causation demonstrated by at least two of the following:
  1 Headache has developed in temporal relation to the onset of the cervical disorder or appearance of the lesion
  2 Headache has significantly improved or resolved in parallel with improvement in or resolution of the cervical disorder or lesion
  3 Cervical range of motion is reduced and headache is made significantly worse by provocative manoeuvres
  4 Headache is abolished following diagnostic blockade of a cervical structure or its nerve supply.

Trochleitis

A Periorbital and/or frontal headache fulfilling criterion C.
B Clinical and/or imaging evidence of trochlear inflammation.
C Evidence of causation demonstrated by at least two of the following:
  1 Unilateral ocular pain
  2 Headache is exacerbated by movement of the eye, particularly downward in adduction
  3 Headache is significantly improved by injection of local anaesthetic or steroid agent into the peritrochlear region
  4 In the case of a unilateral trochleitis, headache is ipsilateral to it.
D Not better accounted for by another ICHD-3 disorder.

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Herpes zoster is much more likely than TN to involve the ophthalmic division. With acute infection, the pain precedes the rash by a few days in most patients, with intervals of up to 100 days being reported (9). Thus, the diagnosis may be delayed for some time before the rash develops. Paraesthesias and dysaesthesias in the affected dermatome may also occur. Spontaneous pain in the acute period (within 30 days of rash onset) is described as constant or nearly constant shooting, stabbing, burning, or electric shock-like (Box 42.2). Similarly to TN, stimulus-evoked pain is common. Postherpetic neuralgia (PHN) persists for 120 days or more after rash onset; remission is unlikely after 180 days. It is the most common complication following acute zoster infection and the incidence increases with age. The pain may be dysaesthetic (spontaneous, constant, deep burning, throbbing, and aching), hyperpathic (intermittent sharp, stabbing, shooting, lancinating pain in response to a stimulus or spontaneous), or allodynic (painful response to an ordinarily non-painful stimulus that persists beyond the duration of the stimulus) (Box 42.2) (8). PHN pain may occur in areas where sensation is lost or impaired *(anaesthesia dolorosa)*.

Laboratory testing

Neuroimaging is performed to exclude a secondary cause of TN (e.g. a lesion in the posterior fossa), identify a compressive vascular loop, and look for evidence of MS in younger patients or those with bilateral TN. Zoster-related neuralgia is diagnosed by history and examination.

Treatment

Carbamazepine is the first-line medical treatment of TN and produces pain relief in 80% of individuals immediately and in the short term. However, relief may not be sustained and many patients do not tolerate the medication. Other agents include baclofen, lamotrigine, pimozide, oxcarbazepine, topiramate, and sodium valproate. Onabotulinum toxin injections targeted at the site of pain are a safe and efficacious emerging treatment (10), with microvascular decompression, gamma knife radiosurgery, and other procedures employed in refractory cases.

Cervicogenic headache as a cause of ocular or periocular pain

Disorders of the upper cervical spine are frequently implicated as the cause of headache, although the relationship of cervical spine

disease and headache is not well validated (see also Chapter 36). There is a physiological basis for this phenomenon, as the upper cervical neurons receive convergent inputs from trigeminal and cervical afferents, and stimulation of cervical afferents sensitizes neurons to trigeminal input in experimental animals. Cervicogenic headache is defined as a headache caused by a disorder of the cervical spine and its component disc and/or soft tissue elements, usually but not invariably accompanied by neck pain. It is often provoked by digital pressure on the neck muscles or by head movement with posterior-to-anterior radiation of pain, sometimes affecting the oculo-fronto-temporal regions. The pain is usually moderate in severity and non-throbbing (11). Headache attributed to upper cervical radiculopathy (C2 and C3) is usually posterior but may radiate more anteriorly (4). It is generally lancinating and may be unilateral or bilateral. The pain of occipital neuralgia may reach the fronto-orbital area.

Some investigators have emphasized suboccipital tenderness as a diagnostic hallmark for these pain syndromes (12) and others have emphasized the importance of unilateral pain that begins as neck pain for the diagnosis of cervicogenic headache (11). One of the defining characteristics of these entities is resolution of the pain with anaesthetic blockade, which may be a confounding feature, as many different types of headaches improve with greater occipital nerve blocks; a potentially causative cervical lesion is often not demonstrated. HC may have similar features.

Laboratory testing

Cervical imaging is specified as per ICHD-3.

Treatment

There are no controlled trials upon which to base treatment recommendations. A trial of indomethacin is warranted if the symptoms suggest HC. Success has been reported with greater occipital nerve blocks, spinal blocks, and manual therapy. Percutaneous rhizotomy and 'liberation' surgery of the nerves provide only temporary relief.

Carotid artery dissection

Dissection of the carotid artery produces pain in the ipsilateral head, neck, face, or jaw. (see also Chapter 37). The pain is frequently located in the forehead or periocular region. The character of the pain varies, and is often described as a constant, non-throbbing pain of gradual onset. However, some patients experience severe, throbbing pain or a thunderclap onset (13). The pain may precede the neurological symptoms by hours, days, or, rarely, weeks. Manifestations include an ipsilateral Horner syndrome, transient monocular visual loss, central or branch retinal artery occlusion, ocular ischaemic syndrome and positive visual phenomena, cranial nerve palsies (III, V, VI), contralateral limb numbness or weakness, or stroke; headache with an ipsilateral Horner syndrome is considered a carotid dissection until proven otherwise (13, 14). Involvement of the nerves emerging from the jugular and hypoglossal foramen produce sternocleidomastoid weakness, hoarseness, dysgeusia, and hemilingual paralysis. Pulsatile tinnitus occurs in < 25% of patients and may be the only presenting symptom.

Carotid dissection may occur at any age, most frequently affecting individuals between 35 and 50 years of age (13). Minor direct trauma or a twisting injury to the neck may precipitate dissection. Abnormalities of the arterial media and elastic tissue, such as Ehlers–Danlos syndrome and fibromuscular dysplasia, predispose to dissection but are seldom found. The major confounding diagnosis of patients with carotid artery dissection is cluster headache, as both conditions may present with a unilateral headache and an ipsilateral Horner syndrome. Any patient with a new onset of cluster headache symptoms lasting longer than the typical duration of cluster headache (2 hours) should be evaluated for a carotid dissection.

Laboratory testing

Preferred imaging techniques are computed tomography (CT) angiography, magnetic resonance angiography, conventional angiography, and axial MRI with fat saturation, which demonstrates the lack of flow void, intramural blood, and mural expansion of the dissection. Doppler imaging may also be helpful.

Treatment

Various treatments are used, although no controlled trials of medical or surgical therapy have been performed. Anticoagulants, antiplatelet treatment, and thrombolytic agents have been employed. Endovascular and surgical treatment are rarely indicated.

Ophthalmic and orbital causes of pain

Trochleitis and primary trochlear headache

The superior oblique tendon and its surrounding fibrovascular sheath pass through the trochlea, a ring-like cartilaginous structure that is innervated by the ophthalmic nerve (15). Inflammation of the superior oblique tendon within the trochlea, or trochleitis, is characterized by local pain, swelling, and tenderness, which worsen with upward gaze in adduction. Palpation of the superiomedial aspect of the orbit provokes exquisite tenderness, and localized trochlear swelling may be felt. The aetiology is most often primary, although trochleitis may accompany rheumatoid arthritis, systemic lupus erythematosus (SLE), sarcoidosis, and other inflammatory disorders. Most often, it is akin to a tendonitis and has been called 'tennis elbow of the eye'.

Primary trochlear headache is distinguished from trochleitis by the absence of inflammation and its common association with other headache disorders, particularly migraine (16,17). It affects women 90% of the time, producing pressure-like or dull pain in the trochlear and temporoparietal regions that worsens with supraduction of the affected eye. There may be nocturnal awakening, but autonomic features are absent (15). Of 25 patients with trochlear headache evaluated at the Mayo Clinic, 22 had a new daily persistent headache (17), characterized as periorbital pain associated with photophobia and aggravated by reading. Five of 12 patients with trochleitis had a secondary cause.

Treatment

The treatment of both conditions is a single injection of corticosteroids (3 mg betamethasone acetate or 0.5 ml methylprednisolone 80 mg/ml, which may be given in combination with 0.3–0.5 ml of 2% lidocaine). Relief occurs rapidly and the patient may be rendered pain-free for months or years. Forty per cent of patients in the Mayo

Clinic series had complete remission after trochlear blocks. The injection may also provide relief of associated migraine pain (16).

Idiopathic orbital inflammation

Idiopathic orbital inflammation (IOI), previously termed 'inflammatory orbital pseudotumour', may occur at any age, presenting with acute, chronic, or recurrent symptoms and signs. Diffuse inflammatory disease typically produces exophthalmos, external swelling, and conjunctival hyperaemia, whereas individuals with specific involvement of the extraocular muscles may present with diplopia and limitation of eye movements (18). The differential diagnosis includes infectious orbital cellulitis, neoplasms with inflammatory signs, and vascular lesions, which may produce similar manifestations. There are granulomatous and non-granulomatous forms of IOI, which may be idiopathic or a component may be part of a systemic disease such as sarcoidosis, tuberculosis, antineutrophil cytoplasmic antibodies-associated orbital granulomatosis with polyangitis, inflammatory bowel disease, IgG4-related disease, dermatomyositis or SLE (19,20).

Orbital pain is a variable symptom, occurring in at least half of affected individuals, and is typically associated with other signs and symptoms depending on the involved orbital structures (18). The pain is often severe and may worsen with eye movement or retropulsion of the globe. Headache or severe eye pain may be present without external inflammatory signs. Orbital ultrasonography is helpful to demonstrate involvement of the posterior sclera, a less common but important form of IOI.

Laboratory testing

Diagnosis requires an ocular and orbital evaluation followed by targeted laboratory studies and radiological imaging, such as CT and fat-saturated and gadolinium-enhanced MRI (21). As lymphoma and other malignancies may have similar manifestations, a biopsy may be required to rule out neoplasia.

Treatment

Treatment includes systemic corticosteroids, other immunosuppressant agents, and radiation therapy (22,23).

Angle closure glaucoma

Acute angle closure glaucoma occurs when the intraocular pressure rapidly rises as a result of closure or blockage of the drainage angle of the eye, the site of aqueous outflow. It may occur in any situation associated with pupillary dilation, which causes the iris to move anteriorly and come into contact with the lens (e.g. emerging from a darkened movie theatre). Risk factors include advancing age, a strong family history of glaucoma, a history of ocular trauma, hyperopia (far-sightedness) and pseudoexfoliation (24). There is a heritable component, as individuals with narrow angles are predisposed, particularly elderly Chinese women. Systemic medications, such as topiramate and medications with anticholinergic properties, are associated with angle closure glaucoma (25).

Typical symptoms are ocular pain, headache, nausea, and vomiting. The attack is often accompanied by blurred vision and patients often complain of seeing halos around lights. Incomplete or mild attacks may abort spontaneously. Therefore, these attacks may be mistaken for migraine. However, unlike migraine patients, patients with acute angle closure will typically demonstrate the following ocular signs:

- Elevated intraocular pressures (typically > 30 mmHg). When tonometry is unavailable, the affected eye may be palpated under closed lids using the thumb pad. A hard, unyielding globe indicates an elevated pressure.
- Conjunctival injection. The eye is typically red and there is often a ring of vascular congestion surrounding the corneal–scleral junction.
- Shallow anterior chamber. The iris is commonly rotated forward towards the back side of the cornea, making the anterior chamber shallower. The angle may be visualized using gonioscopy or optical coherence tomography (24).
- Mid-dilated pupil. The pupil is usually dilated, and either fixed or sluggishly reactive. The combination of pain and dilated pupil angle closure may be mistaken for a third cranial nerve palsy, but the elevated pressure and the lack of ptosis or ocular motor palsy excludes that diagnosis.
- Corneal oedema. The cornea may appear oedematous or cloudy.

Laboratory tests

The diagnosis is made clinically. Ophthalmological evaluation reveals markedly elevated intraocular pressure and angle closure on gonioscopy.

Treatment

While the pain associated with angle closure may improve using analgesics, it quickly subsides once the intraocular pressure is controlled. Intraocular pressure control is usually achieved using cholinergic agents, such as pilocarpine, to constrict the pupil and open the angle. When the intraocular pressure is very elevated (> 45 mmHg), topical medications such as beta blockers and alpha-2 adrenergic agonists, as well as intravenous mannitol and carbonic anhydrase inhibitors, may be needed. Laser peripheral iridotomy is a definitive therapy in nearly all cases.

Ocular surface disease (dry eye)

The cornea contains the highest density of pain receptors in the body with representation in the ventral part of the caudal end of the trigeminocervial complex in the medulla (26). Pain is a common symptom of ocular surface disease that may result from a primary tear film deficiency or abnormality, corneal epithelial disease, contact lens use, and exposure to topical medication, or it may be secondary to systemic inflammatory diseases, including rheumatoid arthritis, Sjögren syndrome, SLE, and psoriasis. It is a common and underdiagnosed cause of ocular pain. Dry eye and pain or redness is a source of dissatisfaction following laser in situ keratomileusis (LASIK). Other common causes of ocular pain are a corneal foreign body, abrasion, or infectious keratitis. Dry eye also occurs with conditions that interfere with normal blinking, such as thyroid eye disease, Parkinson disease, progressive supranuclear palsy, and facial paresis. An underlying cause is not identified in many cases.

Symptoms of ocular surface disease or dry eye may range from a mild discomfort to severe, debilitating symptoms that interfere with activities of daily life. Patients may experience ocular pain, a burning or foreign body sensation, pruritis, redness, reflex tearing, blurred

vision, photophobia, monocular diplopia, or visual distortion. The symptoms often fluctuate and characteristically worsen during activities requiring visual concentration, such as reading, driving, using the computer or smartphone, or watching television.

Examination of the eye using fluorescein dye with a blue light and magnification will quickly identify corneal foreign bodies, abrasions, or keratitis. Abnormalities in the Schirmer sterile test strip evaluation of tear production, vital staining of the corneal surface, and the tear break- up time as viewed with slit-lamp bi-microscopy are helpful in making the diagnosis of dry eye. Therapy for dry eye symptoms includes topical lubricants, anti-inflammatory medications, and punctual occlusion or surgical intervention to prolong ocular tear contact.

Chronic neuropathic corneal pain

The symptoms of corneal neuropathy cause pain that is similar to that of dry eyes, with unremitting burning pain associated with photophobia and, in some cases, reflex blepharospasm (27). This recently recognized entity is characterized by decreased corneal sensitivity as measured by aesthesiometry and a reduced tear lake with normal corneal epithelium on slit-lamp examination. Morphometric analysis of the cornea using in vivo laser scanning confocal microscopy reveals abnormal corneal nerve morphology. The condition is suspected when patients have symptoms of dry eyes but do not respond to standard treatment. It may follow corneal grafting or LASIK procedures. Topical anaesthetics temporarily relieve the pain in some cases (27).

Laboratory testing

In vivo confocal corneal microscopy shows tortuosity, branching, or loss of density of corneal nerves.

Treatment

A fluid-based gas-permeable contact lens that rests entirely on the sclera is the first line of treatment after conventional dry eye treatments fail. Topical lacosamide 1% may be used in the reservoir of the scleral lens if hydration alone is unsuccessful. Scrambler therapy, which synthesizes 16 different types of nerve action potentials to determine a patient-specific cutaneous electrostimulation, works in some refractory patients.

Thyroid eye disease

Thyroid eye disease (TED) is the most common extra-thyroid manifestation of Graves' disease. Approximately 2% of patients with Graves' disease have mild and inactive TED, 6% have moderate-to-severe active TED, and 1% have sight-threatening TED associated with optic neuropathy (28). TED may precede or accompany the thyroid disease and likely represents an expression of the same autoimmune process affecting the thyroid and ocular tissues. It is characterized by oedema and inflammation affecting the lacrimal gland, extraocular muscles, and orbital fat, with a secondary decrease in venous and lymphatic drainage from the orbit (29). TED is much more common in women than in men, and cigarette smoking negatively impacts the course and response to treatment.

Pain commonly occurs in TED, resulting from dry eye and orbital inflammation. Lacrimal gland dysfunction leads to decreased tear production and inadequate corneal lubrication, which may be compounded by proptosis, which increases corneal exposure to air. With severe proptosis and eyelid retraction, there is incomplete blinking and eye closure, causing further corneal dryness. Inflammatory infiltration of ocular tissues may produce constant, aching orbital pain.

The diagnosis is made clinically and the eyes are usually asymmetrically affected. Signs of external involvement include conjunctival injection and oedema, and corneal dryness. The upper and lower eyelids become oedematous and retracted, producing a staring appearance and exaggerating the impression of proptosis. Extraocular muscle involvement, generally affecting the inferior and medical recti first, produces diplopia from restrictive ocular myopathy. Exophthalmos results when the ocular muscle enlargement causes anterior displacement of the globe. While cosmetically distressing and worsening the ocular surface disease, exophthalmos sometimes protects the optic nerve. In patients with 'tight' orbits, there may be limited proptosis and a compressive optic neuropathy results from marked ocular muscle enlargement within the confines of the bony orbit.

Laboratory testing

CT of the orbits reveals increased density of the orbital fat, enlargement of the rectus muscles sparing their tendons, proptosis, slight bowing of the medial orbital wall, and optic nerve compression when present (30). MRI of the orbits provides better tissue differentiation and demonstrates oedema within the orbital structures. Serum markers include thyroid-stimulating hormone receptor antibodies, thyroid stimulating immunoglobulin, and thyroid function tests; euthyroidism does not exclude the diagnosis of TED.

Treatment

Vigorous ocular lubrication (particularly if eyelid retraction or exophthalmos prevents complete blinking or eye closure during sleep), smoking cessation, monocular occlusion to prevent diplopia, and selenium supplementation are first-line therapies. More severe cases with orbital congestion are treated with fractionated radiotherapy (20 Gy total). Corticosteroids may be used, although there is no consensus regarding the optimal dose, route of administration or duration of treatment. Biologics targeting the IGF1R receptor, tocilizumab and rituximab, are being explored (31). Orbital decompression is indicated for patients with optic neuropathy. The active disease runs a course of about 18 months. Afterwards, various surgical procedures, such as orbital decompression, strabismus surgery, and eyelid surgery, are employed to restore a more normal appearance to the eyes, decrease the risk of corneal exposure, and treat the diplopia.

Orbital tumours

Depending on the location in the orbit, orbital tumours may produce pain, proptosis, displacement of the globe, diplopia, optic neuropathy, chemosis, ptosis, leukocoria (in infants), or progressive visual loss. The pain may be ocular, retro-ocular, periocular, or facial, if the trigeminal nerve is affected. Metastatic disease accounts for a small percentage of all orbital tumours, the orbital mass may develop before the primary tumour is diagnosed, and the presentation is usually unilateral. In a large series of 2480 orbital tumours 68% were benign and 32% malignant (32). The frequency of malignancy increased in patients over 60 years of age. Common sources of metastasis are cancer of the breast, lung, thyroid, and prostate. Lymphoma and basal cell carcinoma frequently affect the orbit. The most common orbital tumours of childhood and adolescence are capillary haemangioma, rhabdomyosarcoma, neuroblastoma, optic

nerve glioma, histiocytosis, and cystic lesions. Many tumours in children have an osseous origin, such as fibrous dysplasia, juvenile ossifying fibroma, and osteosarcoma (33). Optic nerve meningioma, adenoid cystic carcinoma, and tumours of the lacrimal gland, and cavernous haemangioma are the most common tumours in patients over 21 years of age. The differential diagnosis includes orbital inflammatory disorders, infections, and thyroid eye disease.

Laboratory testing

Patients suspected of having an orbital tumour should have a complete ophthalmological examination. Imaging is performed using orbital MRI (better for showing detail and soft tissue) and CT (demonstrates bony changes). Orbital echography may be useful in some cases. Fine-needle aspiration of the tumour is sometimes possible to obtain a tissue diagnosis prior to treatment.

Treatment

The treatment is dependent on the tumour type and may include observation, surgical excision, exenteration, corticosteroids, radiation, and chemotherapy.

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43

Orofacial pain

Dental head pains, temporomandibular disorders, and headache

Steven B. Graff-Radford† and Alan C. Newman

Introduction

Orofacial pain involves pain conditions associated with the hard and soft tissues of the head, face, neck, and all the intraoral structures (1,2). The field of orofacial pain encompasses diagnosis and treatment of primary headaches, temporomandibular disorders, neuropathic pain, cervical pain, and myofascial pain (see also Chapter 27) (3). The evaluation and treatment of orofacial pain has evolved into a shared responsibility between the dentist and physician, with considerable overlap, distinguished only by the practitioner's knowledge and training (1,4).

In the International Classification of Headache Disorders published by the Headache Classification Subcommittee of the International Headache Society, orofacial pains are included in the section titled 'Headache or facial pain attributed to disorders of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures'. This section includes the following subsections: 'Headache or facial pain attributed to temporomandibular joint (TMJ) disorder', and 'Headache attributed to other disorders of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth or other facial or cranial structures' (5).

Headache is not exclusively located in the ophthalmic (V1) trigeminal distribution. Rather, headache can present in any part of the head, face, or even the neck (6), which is important diagnostically and therapeutically. Facial pain in the perioral region is often diagnosed as a dental problem without considering referral from a primary headache disorder. The patient may receive dental treatment, without a conclusive diagnosis, resulting in unnecessary treatment and poor outcome. Similarly, primary headache in the face may not be treated by the physician because the pain location is in a 'dental area' and it is assumed it must be odontogenic.

Accurate diagnosis requires a very thorough history, which includes identifying the pain location, quality, intensity, and time course throughout the day, week, and month. We also want to understand alleviating or aggravating factors, whether the pain is spontaneous or triggered, and if there are changes in the pain with posture. Assessment of accompanying symptoms is also important. Once this information is gathered, together with careful examination of the cranial nerves, temporomandibular joints, cervical spine, and dental structures, a diagnosis can be made (7).

The purpose of this chapter is to raise physicians' awareness of orofacial pains so that they can expand their differential diagnosis to include these non-primary headache conditions. We focus on dental pains and temporomandibular pains.

Tooth pains

Tooth pathology pain can present as headache (in the V1 distribution), especially when the affected tooth is located in the maxilla (8,9). Initial pain from tooth pathology can present as headache, although this is unusual. Typically, pain begins in the tooth and then headache may occur secondarily. There can also be simultaneous localized tooth area pain and headache. Painful dental pathology includes tooth decay, tooth cracks, endodontic (nerve) infections, and periodontal disease, although any one of these pathologies can also be non-painful. In the absence of local dental pain a headache diagnosis may be difficult. The physician may be focused on non-dental causes and not look for dental aetiologies. Until there is local dental pain, a reason for the pain may not be elucidated. The patient may be treated with all the usual preventive or abortive medications for headache with limited response. Referral to an orofacial pain specialist may then prompt an evaluation for dental pathology. Physicians should consider the possibility that head pain may be a dental problem, especially when other causes have been ruled out and treatment is unsuccessful or of limited success.

† It is with regret that we report the death of Steven B. Graff-Radford in October 2017.

Dental pathology presenting as headache is explained through trigeminal and central mechanisms with referred pain. A patient with primary headache such as migraine or tension type may see an exacerbation in headache frequency and intensity in the presence of dental pathology. Also, if the patient has a primary headache disorder, tooth pain from dental pathology may worsen. The trigeminal nerves are the common pathway for all head pains (dental, headache, temporomandibular, etc.), and central connections allow for referred pain between the three trigeminal divisions, as well as the upper cervical levels (10,11).

It is more likely that a non-tooth pain presents as toothache rather than vice versa. Medical conditions such as primary headache, sinus disease, and trigeminal neuralgia (TN) can present at toothache (12,13). Afferent nociceptor sensitization can lead to allodynia (pain from non-painful stimuli). This pain starts in the anatomical region where the headache is felt, typically the first division of the trigeminal nerve, and can spread to other parts of the body. Likewise, this can lead to pain in the dental area that is not dental in origin. An example would be an increased sensitivity to tooth pulp testing in a normal healthy tooth (14).

A phenomenon of 'pain remapping' has been described in some patients with migraine, after an insult to the trigeminal system. The insult could be a simple dental filling or major facial trauma. For example, prior to the dental filling the patient may have had bilateral temporal pain, but after the filling a shift of pain to the tooth site occurs. The associated migraine features may also change. This remapping of pain may lead to unnecessary dental treatment and other procedures, as the pain practitioner may not recognize the pain as migraine. Remapping may occur from peripheral afferent input to the second order neurons in the trigeminal nucleus from the location of the injury leading to a central change in processing of the nociceptor signals, leading to a change in pain location of future migraine attacks (15).

Dental caries, or tooth decay, starts in the enamel and the dentin of the tooth but can progress to the neurovascularized pulp of the tooth. At any stage of the decay process there can be pain. This pain can be aching, burning, sharp, pulsatile, or throbbing, and can wake people from sleep. It can be intermittent or continuous. There is often hot and/or cold sensitivity of the tooth or teeth. The duration of pain typically outlasts the time of stimulus. Dental radiographs will usually show the decay, but early stages may not be shown. Some patients have difficulty localizing the pain, which can make the diagnostic process more difficult. Applying heat or ice to the teeth, the use of an electric pulp tester, percussing the teeth with a metal instrument, or palpating the gums around the teeth can help to locate the problematic tooth (16). Dental therapy, such as a filling or a root canal procedure, can then usually be effective.

Once decay has spread to the pulp of the tooth, the infection can travel though the entire neurovascular root canal system. This can result in extravasation of the infection out of the apex of the root or roots and appear as a periapical endodontic lesion, which presents as a radiolucency on radiographs. This infection can be painful or non-painful. Pain upon chewing or percussion is a classic sign of periapical pathology. Eventually, the pulp can become necrotic and become painless. Treatment is with endodontic root canal therapy where the pulp is removed and replaced with an inert material called gutta-percha. Dependent on the level of pulp pathology, the diagnosis may be reversible or irreversible pulpitis.

A cracked tooth can present like TN with brief, sharp shooting pain when pressure is applied, which opens the crack. The pain is usually triggered with chewing food or teeth grinding. It is usually not spontaneous, as in TN. Using a tooth sleuth (a specialized plastic bite stick) can help find cracks. When the patient bites on the tooth sleuth and gets pain upon releasing a crack may be present. Standard dental radiographs, such as periapical films, which are two dimensional, can show large cracks or cracks that are in the plane of the X-ray beam but often do not show many cracks (17). The use of a three-dimensional cone beam computed tomography (CBCT) scan is more likely to show cracks then conventional films (17). A cracked tooth may be repairable with restorative treatment or may need to be extracted (18).

One way to help differentiate between a dental problem and a primary headache syndrome is by local anaesthetic blockade. If dental pathology is suspected, a local infiltration of anaesthetic at the tooth site should block the pain. If the pain does not resolve with anaesthetic blockade, another pathology should be suspected.

Neuropathic pain can also be confused with dental pathology. TN presents as brief electric shocks of pain typically in the second or third trigeminal nerve distributions and often around the teeth. TN is almost always one sided, and is often triggered by stimuli such as brushing the teeth, washing the face, shaving, or having a breeze blow across the skin of the face. It is typically quiescent at night. Pain caused by dental pathology differs in that it can occur during the night, and as described , can be triggered by hot or cold foods. With TN, the temperature of food usually is not a provoking factor. Pain when chewing can also be seen with TN (19).

Periodontal disease involves inflammation and infection of the gingiva, alveolar bone, periodontal ligament, and cementum. If untreated, periodontal disease can lead to bone loss, tooth mobility, and, eventually, tooth loss. Pain is usually associated with later stages of the disease, although there can be pain earlier on. The cause of periodontal disease is from plaque deposits on the teeth. Such a plaque is made up of bacteria, mucus, and food debris, leading to inflammation and irritation of the gums. Treatment includes debridement, antibiotics, and sometimes surgery.

Temporomandibular disorders

Temporomandibular dysfunction refers to disorders of the temporomandibular joint (TMJ) and associated structures. This includes painful and non-painful conditions. Painful temporomandibular disorders may be associated with headache and pain in the distribution of the trigeminal, upper cervical, and glossopharyngeal nerves (20,21).

Temporomandibular dysfunctions (TMDs) include TMJ arthritis, TMJ capsulitis, TMJ internal derangement, TMJ trauma, TMJ dislocation, myalgia, myofascial pain, spasm, and trismus.

TMJ pain is reported in 10% of the population (22). TMD may occur in up to 46% of the population (23). These statistics show how TMDs can be a major contributor to the number of people with head or face pain. Physicians and dentists need to be aware of this and examine the TMJ system as part of their pain evaluation. The measure to which headaches and TMDs have a causal role with each other, however, is not known. It is possible that treating TMD's can help to relieve headaches and vice versa.

The subjective complaint of headache may be the only presentation for patients with TMDs. Muscle or joint pain can present as headache and/or exacerbate headache. Headache and TMDs are often comorbid (24).

Myalgia and myofascial pain are muscular TMDs if the pain affects the muscles around the TMJs. The muscles most commonly involved are the masseters, temporalis, and pterygoids There may be no joint-specific subjective or objective findings, but a TMD can be considered if the muscles are involved with movement of the jaw. Myalgia is muscle pain that can arise from trauma such as a blow to the face or from overuse such as from fingernail biting, or gum chewing or overstretching of the jaw. Other aetiological factors can be bruxism and emotional and behavioural stressors. Treatment may include rest, a soft diet, moist heat applications, massage, physical therapy, muscle relaxants, topical non-steroidal drugs or analgesics, a bite guard, and trigger point injections (25). If the pain persists and becomes chronic it may be harder to treat. If the cause is ongoing parafunction (clenching or grinding teeth, gum chewing) the pain may not improve until the parafunction ceases.

Myofascial pain is regional muscle pain, the hallmark of which is muscle pain points at pressure with referral to areas of different dermatomal distribution from the original pain site (26). These pain points, also known as trigger points, are localized areas in the muscle, tendon, or fascia that are felt as taught bands. When active, palpation of trigger points can refer to other areas (27). For example, palpating the trapezius can cause pain in the temporalis muscle area. The mechanisms for the pain referral of myofascial pain are thought to be through central sensitization. In addition to remote pain referrals, myofascial pain can be accompanied by disturbed sleep, dizziness, tinnitus, memory issues, sweating, numbness, stuffy nose, runny nose, and blurry vision, associated features that can confuse the diagnosis. Myofascial pain is described as a deep ache, burning or sore, but may also be shooting or throbbing. Management of myofascial pain is best achieved with physical medicine techniques, exercises, injections, and medications (25). Typically, muscle relaxant, non-steroidal anti-inflammatory drugs, and tricyclic antidepressant medications are used (25). The usefulness of these medications is through their central actions. Injecting the trigger point with local anaesthetic will reduce the pain and can be helpful diagnostically and therapeutically (25).

When examining a headache patient it is imperative to do a muscular examination that includes palpation of the muscles of the head and neck. If muscles are painful on palpation, the patient should be asked if that pain is the same as the chief complaint or not. If there is a muscular component, treatment should be as listed earlier. In patients that have headaches and muscle pain, treatment of the muscle component can reduce headache frequency and intensity.

The TMJ is a ginglymoarthrodial synovial joint, thus having a dual function joint, as it both hinges and glides. It has both an upper and lower compartment separated by an articular disc. Its innervation is mainly from the auriculotemporal branch of the mandibular nerve (28). The joint is also made up of the condyle of the mandible and the temporal bone fossa.

Inflammation causes joint pain, the potential aetiologies of which are a trauma, bruxism, emotional and behavioural stressors, low serum oestradiol levels, and autoimmune diseases (29). The cause can also be idiopathic.

Macro-trauma would be injury from a single application of force such as being struck on the face. The injury can be acute and resolve quickly, or can become chronic. Micro-trauma results from repetitive overuse such as from frequent chewing of gum, nail biting, and clenching and grinding the teeth. Micro-traumas are often referred to as 'habits'. Repetitive movements can cause joint inflammation leading to pain and eventually the breakdown of the joint components. They also cause micro-tearing of muscle fibres, the sheath around the muscles, and the connective tissue. Over time, the trauma causes damage to the orofacial structures and pain and/or dysfunction.

TMJ arthritides include osteoarthritis (OA), rheumatoid arthritis (RA), traumatic arthritis, and infectious arthritis (30).

OA or wear-and-tear arthritis is the most common type of arthritis of the TMJ. Complaints of pain with function and crepitation sounds are common. Imaging shows flattening of the articular surfaces. Cyst formation of the condyle(s) and/or temporal bone can occur.

RA of the TMJ occurs in around 17% of adults and children with RA. The most common findings are pain, swelling, and restricted range of motion. Ankylosis is a possible sequalae of RA of the TMJ (24). Imaging may show irregular articular surfaces, although early stages may look similar to OA.

TMJ internal derangements are disc condyle complex incoordination and disc displacement, with or without reduction. In either case, noise in the joint is the hallmark. There may or may not be pain. In disc displacements, the disc that normally accounts for stability in the TMJ becomes displaced, resulting in an incoordination. Alteration in the disc morphology and changes to the retrodiscal ligament can lead to the displacement and tissue breakdown.

In disc displacement with reduction, the disc assumes its normal position during mouth opening, which results in a click type of noise. It may also lose its normal position upon closing and then a 'reciprocal' click may be heard. In disc displacement without reduction, the disc does not go back to its normal physiological position and stays displaced. Then, no noise is heard.

The quality of TMD pain varies from the dull, aching sensation of muscular pains to the potentially sharp, shooting pain of arthritides and disc derangements. In some instances there is no pain, only noises in the joint or locking.

Diagnostic imaging may be necessary to detect fractures, arthritides, and derangements (31). A computed tomography scan (ideally a CBCT) will show fractures and arthritis if present. MRI shows disc position quality and function, joint effusion, arthritic changes, and fractures. A CBCT scan is better at viewing the bony structures, whereas MRI is better for viewing soft tissues. Sometimes both are needed. A panoramic X-ray can give a quick overall idea of the condition of the bony surfaces.

Treatments for TMDs should follow a medical and not a dental model of care, including habit avoidance, rest, heat, ice, physical therapy, medications, injections, cognitive behavioural therapy, occlusal guards, and acupuncture. Dental treatments such as occlusal adjustments or tooth restorations are irreversible and not warranted. Conservative treatment often significantly improves or resolves TMDs.

In summary, there are relationships between headaches and dental disease, and headaches and TMDs. It is imperative that the

clinician is aware of these relationships, and takes the history and examines the patient with these in mind. If the clinician is unsure of the pain diagnosis the patient should be referred to an orofacial pain dentist who can help make the diagnosis and treat the pain, whether it is dentally based or not.

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44

Headache with neurological deficits and cerebrospinal fluid lymphocytosis (HaNDL) syndrome

Germán Morís and Julio Pascual

Introduction

In 1951, Symonds described a man who had stereotyped spells of visual loss and unilateral weakness, followed by headache, drowsiness, and vomiting (1). Associated with these symptoms were increased cerebrospinal fluid (CSF) pressure and pleocytosis. Each attack lasted several days and resolved without sequelae. Similar cases were subsequently reported, but it was not until 1981 that Bartelson and colleagues coined the term 'migrainous syndrome with CSF pleocytosis' (2). These authors described a series of patients who had migraine-like attacks accompanied by sensory, motor, speech, and visual disturbances in addition to CSF abnormalities, and they provided a literature review of similar cases. In 1984, Martí-Massó published a series of cases in a Spanish journal (3). After reviewing available cases and adding seven patients with a similar presentation, in 1995 Berg and Williams proposed the term 'headache with neurologic deficits and CSF lymphocytosis' (HaNDL) (4). Subsequently, Gomez-Aranda and colleagues described a series of 50 patients with this syndrome and called it 'pseudomigraine with temporary neurological symptoms' (5). Some reviews include the early descriptions of Spanish cases (6,7).

Epidemiology

Approximately 100 HaNDL cases have been reported in the literature, which suggests that the syndrome is rare. Its exact incidence is unknown as no epidemiological studies have been reported. However, HaNDL is probably underdiagnosed because of the unfamiliarity with the disorder (8). In our experience in Spain, and after actively looking for these cases for more than 10 years, the incidence of HaNDL is estimated to be approximately 0.2 cases per 100,000 inhabitants per year. Even though this syndrome has been mainly described in the south of Europe and in the USA, we are aware of HaNDL cases in many other countries. For instance, a Japanese case was reported in 2003 (9).

HaNDL is more frequent in men (3:1) (5,10). Reported ages at onset ranged from 7 to 50 years, but most patients are around 30 years of age at onset (5,10), although some authors have recently suggested that HaNDL is underdiagnosed in children (11).

Clinical presentation

By definition, HaNDL syndrome is a self-limited syndrome that is characterized by a sudden onset of headache with temporary neurological deficits and CSF lymphocytosis (4,5,9). The diagnostic criteria of HaNDL, according to the new International Classification of Headache Disorders, third edition (ICHD-3), classification of the International Headache Society, are presented in **Box 44.1** (12).

Up to 3 weeks prior to the onset of headache, about one-third of patients report cough, rhinitis, diarrhoea, and/or generalized malaise. The majority of patients describe their headache as severe, throbbing, oppressive, or of a type not previously experienced (5). However, some patients experience episodes with only mild or no headache (5,13). The pain may be bilateral or hemicranial, lasting from 1 hour to 1 week (mean 19 hours), and may be accompanied by nausea, vomiting, photophobia, or phonophobia. Most patients with HaNDL do not report a history of migraine headaches.

The temporary neurological deficits of this syndrome are characteristic and differ from those seen in migraine auras (14). Eighty per cent of patients with HaNDL have transient neurological deficits restricted to one hemisphere. The remaining 20% have either episodes affecting different brain regions (5). Three-quarters experience deficits in the dominant hemisphere. In our opinion, this phenomenon is due to a higher clinical awareness of dysfunction in this hemisphere. Right hemisphere spells may pass unnoticed. In patients with multiple episodes in one hemisphere, the neurological deficits were not always the same in different episodes (5). Transient neurological deficits last between 5 minutes and 1 week

Box 44.1 Diagnostic criteria of HaNDL

- **A** Episodes of migraine-like headache fulfilling criteria B and C.
- **B** Both of the following:
  - **1** Accompanied or shortly preceded by the onset of at least one of the following neurological symptoms lasting > 4 hours:
    - (a) Hemiparaesthesia
    - (b) Dysphasia
    - (c) Hemiparesis
  - **2** Associated with CSF lymphocytic pleocytosis (> 15 white cells per µl), with negative aetiological studies.
- **C** Evidence of causation demonstrated by either or both of the following:
  - **1** Headache and transient neurological deficits have developed or significantly worsened in temporal relation to the CSF lymphocytic pleocytosis, or led to its discovery
  - **2** Headache and transient neurological deficits have significantly improved in parallel with improvement in the CSF lymphocytic pleocytosis.
- **D** Not better accounted for by another ICDH-3 diagnosis.

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(mean 5 hours); only one patient had aphasia that lasted longer than 1 week. Sensory symptoms (78% of episodes), language disorders (60%), and hemiparesis (56%) are the more frequent focal deficits. Sensory symptoms are described as numbness that frequently starts in the hand, progresses through the arm, and then affects the face and tongue, with the legs rarely involved. Pure motor aphasia is the most frequent speech disorder (36% of episodes), followed by global aphasia (22%) and pure sensory aphasia (2%). Diffuse manifestations in the form of confusion may be part of the clinical expression (15,16). Visual symptoms occur in a lower percentage (10%) than in migraine aura. Seizures are infrequent. The most common combinations of focal symptoms are motor aphasia plus sensory and motor right hemibody symptoms, motor aphasia plus right sensory symptoms, and isolated sensory symptoms in one hemibody. Approximately 50% of patients also have nausea and vomiting: some of them also experience phonophobia and photophobia. Fever occurs in 25% of patients and coincides with the episodes. Meningeal signs have not been reported (5).

Patients are asymptomatic between episodes. The described number of episodes per patient ranges from 1 to 12 (median 2) and the duration is always shorter than 3 months. All patients with HaNDL reported recovered completely within 1 to 84 days. The only reported complications were related to the diagnostic work-up, especially cerebral angiography, and not to the syndrome itself. All reported patients with HaNDL have recovered completely. The syndrome is self-limiting and thus far recurrence has not been reported (2,4,5,10).

Aetiology and pathophysiology

The aetiology of HaNDL is unknown. A viral aetiology, such as an Epstein–Barr virus (EBV) infection, aseptic vasculitis, and migraine, have been proposed, although none is proven to date.

Although the age of patients with HaNDL syndrome coincides with that of the maximum incidence of migraine, there are a number of differences between migraine and this monophasic syndrome. Some of the headache characteristics differ from those seen in migraine. The duration of temporary deficits (5 hours on average) in HaNDL is longer than the typical aura duration in migraine (< 1 hour). In migraine with aura visual symptoms are the most frequent, followed by sensory, aphasic, and motor symptoms, which is exactly the opposite in HaNDL (14). A constant feature of HaNDL is (by definition) CSF lymphocytic pleocytosis. CSF pleocytosis of more than 10–15 mononuclear cells/mm^3 does not occur in migraine with aura, or even in the most severe forms of stuporous migraine or hemiplegic migraine (17–20).

There are many infectious conditions that may present with temporary neurological deficits, headache, and CSF lymphocytic pleocytosis. Clinical and complementary data must rule out conditions such as Lyme disease, neurosyphilis, neurobrucellosis, mycoplasma infections, human immunodeficiency virus (HIV) meningitis, and granulomatous and neoplastic arachnoiditis, that could theoretically account for clinical symptoms such as those observed in HaNDL. However, despite extensive viral serological evaluation, viruses have been very rarely detected. These data, together with the absence of meningeal irritation during and between episodes, seem to rule out conventional viral meningoencephalitis as its aetiology, although it still appears reasonable to search for neurotropic viruses in selected cases.

If migraine and infectious meningoencephalitis do not explain HaNDL, what else could be its cause? We have proposed that HaNDL could be an autoimmune disorder, conceptually similar to (for instance) Guillain-Barré syndrome (**Figure 44.1**). Approximately one-third of patients with HaNDL have symptoms of a 'viral' illness in the preceding 3 weeks. It is possible that such an infection could trigger the immune system, producing antibodies to neuronal or cranial vessel antigens. This may induce the transient neurological symptoms throughout a spreading depression-like mechanism and then aseptic vasculitis, which would account for the 'vascular' headache and CSF pleocytosis (21,22). It has been shown that intravenous administration of high-dose immunoglobulins induces aseptic meningitis, manifested as headache and sometimes accompanied by transient focal symptoms, in approximately 10% of patients. Interaction between immunoglobulin G (IgG) alloantibodies and endothelial antigens in cranial vessels has been proposed to be the cause for this complication (23). Supporting this hypothesis, antibodies to a subunit of the T-type voltage-gated calcium channel CACNA1H have been described in the sera of two of four patients with HaNDL (24).

Differential diagnosis

The diagnosis of HaNDL is made after excluding more common conditions that present with headache and transient neurological signs and symptoms. HaNDL can be confused with migraine, particularly hemiplegic and basilar migraine, but migraine normally is not associated with CSF lymphocytosis (25). Patients with

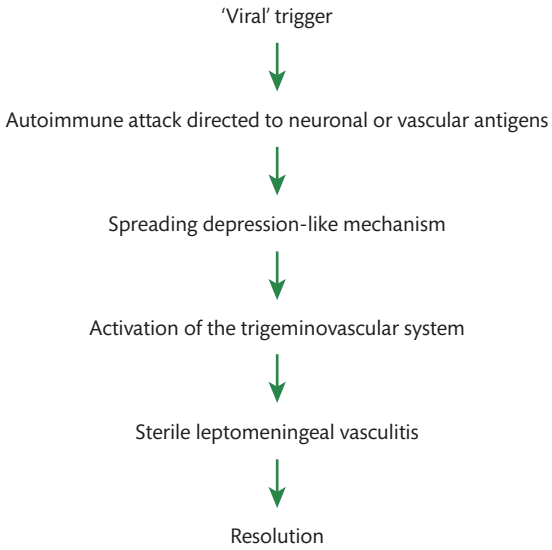

Figure 44.1 Putative pathophysiology of headache with neurologic deficits and cerebrospinal fluid lymphocytosis (HaNDL).

hemiplegic aura usually have a positive family history (familial hemiplegic migraine) (see Chapter 8), and a study of mutations in the *CACNA1A* gene in HaNDL cases was negative (26). Patients with basilar migraine may have a similar presentation (2), but recurrent symptoms topographically consistent with the basilar artery territory, a history of other types of headaches, and a good response to antimigraine therapy will usually help in differentiating basilar migraine from HaNDL. The syndrome described as 'migraine associated with focal cerebral oedema, CSF pleocytosis, and progressive cerebellar ataxia' usually recurs over many years and is associated with cerebral oedema, which can be documented on magnetic resonance imaging (MRI) and is different from HaNDL (27). The first episode of HaNDL can mimic an acute ischaemic stroke (see Chapters 10 and 37), leading to the consideration of systemic thrombolytic therapy (28–31). Normality of diffusion-weighted MRI images in the acute phase is an important clue for diagnosis in these cases (32).

Other conditions that present with headache, CSF lymphocytosis, and transient neurological symptoms, and signs include viral meningitis, Mollaret meningitis, neuroborreliosis, neurosyphilis, neurobrucellosis, mycoplasma infection, neoplastic meningitis, granulomatous meningitis, autoimmune disease (33), and HIV infection (see Chapter 41). Appropriate laboratory studies and brain imaging help to exclude these conditions and should be performed before making a diagnosis of HaNDL.

Multiple sclerosis can be confused with HaNDL, particularly when a first episode manifests as focal neurological symptoms with headache. The clinical course, presence of oligoclonal bands, and abnormal immunoglobulin synthesis in the CSF will distinguish this disease from HaNDL.

Occasionally, seizures and status epilepticus present with focal signs (Todd's paralysis) and CSF lymphocytosis (see Chapter 12) (34,35). When the seizures are witnessed, distinguishing them from HaNDL is not difficult, but in the event of unwitnessed spells, an electroencephalography (EEG) may be helpful (36).

Diagnostic work-up

The diagnostic work-up of HaNDL should be focused on excluding other, more common, and less benign disorders. Routine laboratory determinations, including immunological studies, are within normal limits in most cases. In very few cases, a slight leucocytosis, increased levels (<100 U/L) of transaminases, or positive antinuclear antibodies (< 1/80) have been reported. Serologies or cultures for virus, *Brucella, Borrelia, Mycoplasma, Treponema*, and tuberculosis are negative, but HaNDL-like syndromes have been described as a result of cytomegalovirus, EBV, and herpervirus 6 infections (19,36,37).

CSF opening pressure is elevated in more than 50% of HaNDL cases. CSF glucose is always normal. Reported CSF pleocytosis ranges from 10 to 760 cells/mm^3 (mean 200 cells/mm^3), with a clear lymphocytic predominance. Protein levels are elevated in more than 90% of cases (mean 94 mg/dl; maximum 250 mg/dl). IgG and adenosine deaminase levels are within normal limits and oligoclonal bands are absent. If performed, other CSF studies, including bacterial, viral fungal, and immunological studies, are invariably normal (4,5).

A good-quality imaging study to rule out a space-occupying lesion (computed tomography (CT) or preferably MRI) should be the first step in the diagnostic work-up of HaNDL. The only abnormality sometimes observed on MRI in patients with HaNDL is non-specific T2 hyperintensity, which can also be seen in patients with migraine (4,5). Magnetic resonance diffusion-weighted imaging during temporary focal symptoms was initially reported to be normal (38), but recent reports have shown a complete hemispheric perfusion/diffusion mismatch (39,40). This finding, together with a normal MRI angiogram, should therefore raise the suspicion of HaNDL. Changes in blood flow accompanied by changes in vessel pulsatility, which are liable to be interpreted as a traumatic brain injury pattern consistent with occlusion and embolism, have been described with transcranial Doppler (39,41,42). Conventional cerebral angiograms do not help in the diagnosis as they are usually normal or show non-specific abnormalities, even in the symptomatic phase. Occasionally, irregularities suggestive of vessel wall inflammation have been described in opercular arteries. Angiograms must, however, be avoided as they can trigger new episodes (4,5).

During the episodes, more than two-thirds of patients with HaNDL show unilateral EEG slowing over the symptomatic side (43,44). Up to 1 day after the episodes, a brain single-photon emission CT (SPECT) usually detects focal areas of decreased radionuclide activity, which is coincident with the neurological symptoms. SPECT becomes normal within 2 days after the transient neurological symptoms (**Figures 44.2 and 44.3**) (5,45).

Treatment

It is important to recognize this benign syndrome in order to avoid unnecessary testing, such as cerebral angiography. Its self-limiting character, including a complete resolution of all symptoms and laboratory abnormalities and a lack of recurrence indicate that only symptomatic and supportive treatment may be needed. No treatment options have been reported either to abort the acute episodes or to prevent its recurrence.

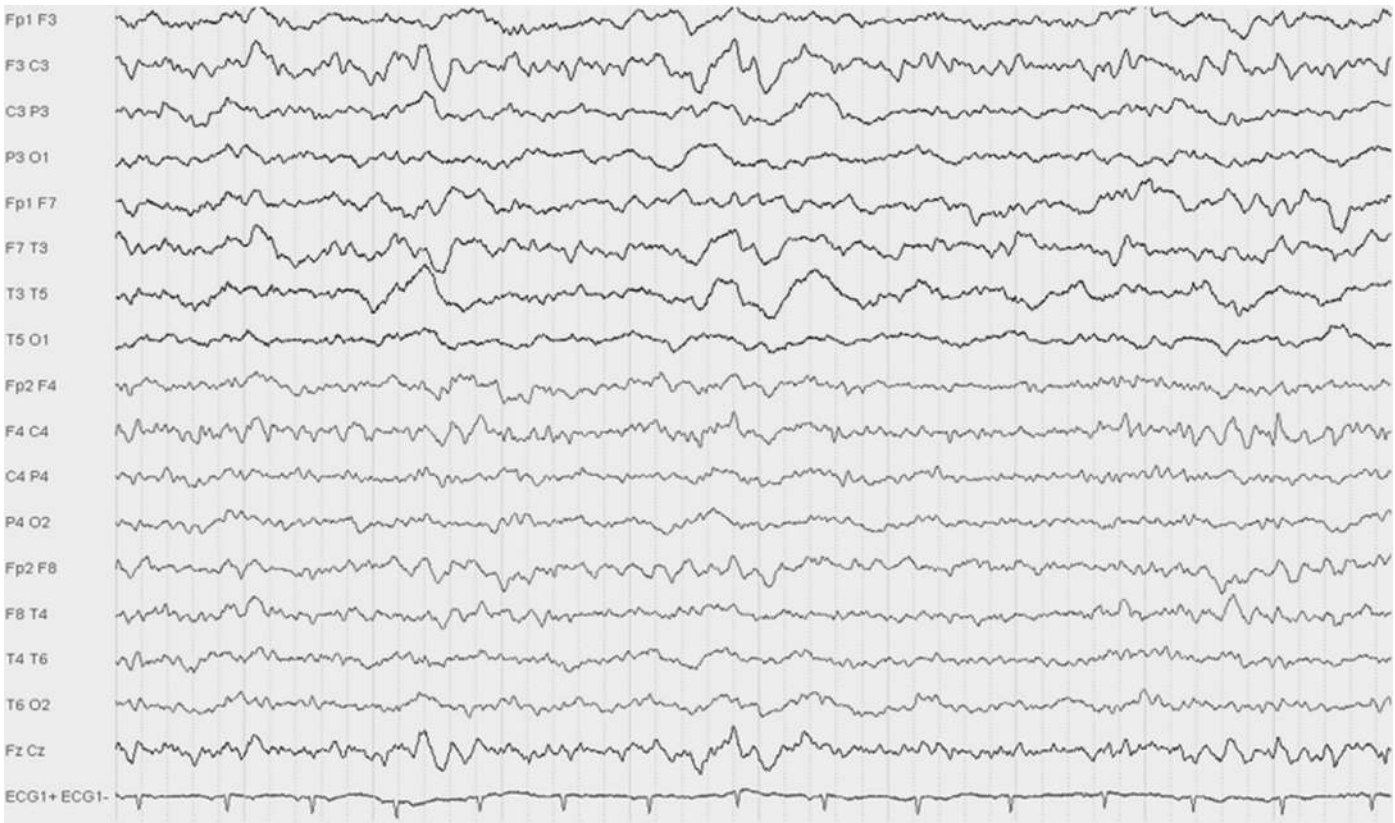

Figure 44.2 Electroencephalogram of the same patient as in Figure 44.3 showing slow waves over the left hemisphere. A further study 3 days later was unremarkable.

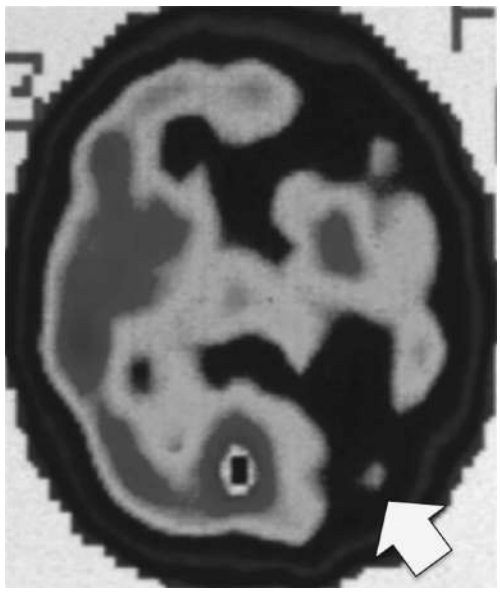

Figure 44.3 (see Colour Plate section) Single photon emission computed tomography (SPECT) image in a typical patient with headache with neurologic deficits and cerebrospinal fluid lymphocytosis (HaNDL) 16 hours after an episode of headache accompanied by right motor and sensory symptoms and global aphasia showing decreased tracer uptake in the left hemisphere (arrow). A SPECT study carried out 3 days later was normal.

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45

Nasal and sinus headaches

Vincent T. Martin and Maurice Vincent

Introduction

Very few topics in the headache field engender more controversy than nasal and sinus headache. Patients often believe that their headaches are attributed to these disorders because they experience rhinitis symptoms (e.g. rhinorrhoea, nasal congestion, and postnasal drip) during their attacks. Primary care physicians, otolaryngologists, and allergists often diagnose nasal and sinus headaches and treat them with rhinitis medications, antibiotics, allergy shots, and surgical interventions, with varying levels of success. In contrast, most neurologists and headache specialists believe that many patients with a diagnosis of sinus headache are suffering from migraine or another primary headache disorder.

History

In 1908 Sluder described patients with severe rhinosinusitis of the ethmoid or sphenoid sinus that later developed a pain in the upper jaw, teeth, orbit, ear, and mastoid region accompanied by ipsilateral parasympathetic symptoms (e.g. nasal obstruction, lacrimation, conjunctival injection) (1,2). In addition, some of the patients experienced nausea, fortification spectra, and vertigo with these headaches. He postulated that that the sphenopalatine ganglion was damaged by toxins from the rhinosinusitis. Furthermore, he attempted to destroy the sphenopalatine ganglion by injecting it with phenol to treat this condition (3). This syndrome was later termed 'Sluder's neuralgia' or 'sphenopalatine ganglion neuralgia' (3,4). Considering the non-uniform location of the headaches, the presence of autonomic and migrainous symptoms, and the clustering of attacks it is quite probable that many of the patients with 'Sluder's neuralgia' may have been suffering from migraine or cluster headache.

In 1943 McAuliffe and Wolfe performed experiments in which they applied an electrical stimulus to various structures of the nose and paranasal sinuses and asked patients to record the locations of pain after these stimuli (5). They found that pain was referred to very specific areas depending upon which locations were stimulated (Table 45.1). The most common regions of referred pain included the frontal, temporal, orbital, nasal, and medical canthal regions of the head. The results from this study have been used by otolaryngologists to bolster their contention that disorders of the nose and paranasal sinuses can cause facial pain and headache. However, a more recent study could not corroborate these results and found that application of a pressure stimulus or substance P to the nasal mucosa only produced local discomfort and did not produce the referred pain, as noted in McAuliffe's study (6).

What are sinus headaches?

There are no formal diagnostic criteria for 'sinus headache', as proposed by the International Classification of Headache Disorders, third edition (ICHD-I3). Most of the past epidemiological studies have based a diagnosis of sinus headache on the belief by the patient or his/her treating physician that abnormalities of their sinuses were causing their headaches. Not surprisingly, these studies have included a high percentage of patients with symptoms of rhinitis. In fact, one study (7) found sinus pressure, nasal congestion, and rhinorrhoea in 84%, 63%, and 40%, respectively, of 2396 patients with a concomitant diagnosis of sinus headaches and migraine.

There are several reasons to support the contention that so-called 'sinus headaches' simply represent variants of migraine. Firstly, attacks of migraine are commonly located in the frontal, orbital, glabellar, and temporal regions of the head, which are locations overlying or adjacent to the paranasal sinuses. Secondly, cranial parasympathetic symptoms (e.g. lacrimation, rhinorrhoea, nasal congestion) occur in up to 40–45% of migraine attacks and their presence could cause physicians and patients to incorrectly assume that their headaches originate in their sinuses (8,9). Thirdly, studies have demonstrated a prevalence of migraine headache ranging from 68% to 88% in patients with self-reported sinus headache, and these headaches tend to respond to migraine-specific abortive medications (7,10–15). However, these data do not preclude the possibility that disorders of the nose and paranasal sinuses could, indeed, produce headache/facial pain or modulate the frequency and disability of existing primary headache disorders.

Table 45.1 Summary of McAuliffe's study of electrical stimulation of the nose and paranasal sinuses.

Site of stimulation	Pain intensity	Location of pain
Nasal septum	1–2+	Zygoma, pre-auricular, inner canthus
Superior turbinate	–	Medical canthus, forehead, lateral nose
Inferior turbinate	4–6+	Upper teeth, zygoma, ear, under eye
Middle turbinate	4–6+	Zygoma, ear, temple
Maxillary ostium	6–9+	Nasopharynx, molars, temple
Frontal sinus	1–2+	Forehead
Ethmoidal sinus	5–6+	Over eye, medial canthus, upper jaw, deep in eye, upper teeth, lateral nose
Maxillary sinus	–	Eye, jaw, molars
Sphenoid sinus	5–6+	Deep in head, over eye, upper teeth, vertex

Adapted from *Research publications - Association for Research in Nervous and Mental Disease*, 23, McAuliffe G, Goodell H, and Wolff H. Experimental studies on headache: pain from the nasal and paranasal sinuses, pp. 185–208. 1943.

Headache attributed to disorders of the nose and paranasal sinuses

Headaches attributed to disorders of the nose and paranasal sinuses have recently been recognized within the diagnostic criteria of ICHD-3 as causes of facial pain and headache. The ICHD-3 criteria for headaches associated with rhinosinusitis (acute and chronic/recurring types) and disorders of the nasal mucosa, turbinates, or septum are shown in Boxes 45.1 and 45.2. Note that there must be clinical, nasal endoscopic, or imaging evidence of the disorder, as well as proof that the disorder is causing the headaches.

Innervation of the nose and paranasal sinuses

The nose and maxillary sinuses are richly innervated by branches of the ophthalmic (V1) and maxillary (V2) divisions of the trigeminal nerve, which could provide an anatomical basis to explain the pain and headache encountered with disorders of the nose and sinuses (16). The anterior ethmoidal nerve is a branch of V1 and innervates the anterior septum and anterior part of the lateral nasal wall. Branches of V2 traverse the sphenopalatine foramen and form the nasopalatine nerve that innervates the inferior part of the nasal septum. The infraorbital nerve arises from V2 and is encased in a bony canal in the roof of the maxillary sinuses. The superior, middle, and inferior alveolar nerves are branches of the infraorbital nerve and innervate the maxillary sinus.

Specific disorders

There are a number of specific disorders of the nose and sinuses that have been associated with headaches in the literature (Table 45.2) (17). Examples of sinus disorders that are associated with headache include rhinosinusitis, dehiscence of the infraorbital nerve, vacuum

Box 45.1 ICHD-3 diagnostic criteria for headache attributed to acute rhinosinusitis

- **A** Any headache fulfilling criterion C.
- **B** Clinical, nasal endoscopic, and/or imaging evidence of acute rhinosinusitis.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of rhinosinusitis
  - **2** Either or both of the following:
    - (a) headache has significantly worsened in parallel with worsening of the rhinosinusitis
    - (b) headache has significantly improved or resolved in parallel with improvement in or resolution of the rhinosinusitis
  - **3** Headache is exacerbated by pressure applied over the paranasal sinuses
  - **4** In the case of a unilateral rhinosinusitis, headache is localized and ipsilateral to it.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 45.2 ICHD-3 diagnostic criteria for headache attributed to chronic or recurring rhinosinusitis

- **A** Any headache fulfilling criterion C.
- **B** Clinical, nasal endoscopic, and/or imaging evidence of current or past infection or other inflammatory process within the paranasal sinuses.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of chronic rhinosinusitis
  - **2** Headache waxes and wanes in parallel with the degree of sinus congestion and other symptoms of the chronic rhinosinusitis
  - **3** Headache is exacerbated by pressure applied over the paranasal sinuses
  - **4** In the case of a unilateral rhinosinusitis, headache is localized and ipsilateral to it.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Box 45.3 ICHD-3 diagnostic criteria for headache attributed to the nasal mucosa, turbinates or septum

- **A** Any headache fulfilling criterion C.
- **B** Clinical, nasal endoscopic, and/or imaging evidence of a hypertrophic or inflammatory process within the nasal cavity.[1]
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to the onset of the intranasal lesion, or led to its discovery
  - **2** Headache has significantly improved or significantly worsened in parallel with improvement in (with or without treatment) or worsening of the nasal lesion
  - **3** Headache has significantly improved following local anaesthesia of the mucosa in the region of the lesion
  - **4** Headache is ipsilateral to the site of the lesion.
- **D** Not better accounted for by another ICHD-3 diagnosis.

Note

[1]Examples are concha bullosa and nasal septal spur.

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Table 45.2 Specific disorders of the nose and sinuses that are associated with headache.

Types of disorders	Examples
Sinuses	Acute and chronic sinusitis Vacuum headache Dehiscence of the infraorbital nerve Airplane headache
Nasal, turbinates and septum	Chronic rhinitis Impacting nasal spurs Middle and superior turbinate syndrome Other anatomic abnormalities
Other	Mid-segment facial pain

headaches, and airplane headaches. Nasal disorders include chronic rhinitis, mucosal contact points, and other anatomical abnormalities of the nose and sinuses. In the following sections, we will discuss the diagnosis, epidemiology, pathophysiology, and treatment of these disorders, as well as the scientific evidence linking these disorders to headache and facial pain.

Acute and chronic rhinosinusitis

Acute and chronic rhinosinusitis are defined as inflammatory conditions of the paranasal sinuses. In the past, rhinosinusitis was simply thought to represent an infection of the paranasal sinuses, but recent work has also implicated inflammatory mechanisms in its pathogenesis, as atopy occurs in 25–70% patients with this disorder (18). Nasal polyps are thought to arise from mucosal inflammation in the nares and therefore rhinosinusitis may exist both with and without nasal polyps.

The definitions of acute and chronic rhinosinusitis as developed by the American Academy of Otolaryngology are listed in Table 45.3 (19). Note that the cardinal symptoms of rhinosinusitis include purulent nasal drainage, facial pain/pressure, and nasal obstruction. Acute rhinosinusitis (ARS) lasts for less than 4 weeks, while chronic rhinosinusitis (CRS) lasts for longer than 3 months (20).

ARS is one of the most common conditions encountered by primary care physicians, accounting for 20 million office visits per year in the USA (22). CRS occurs in 2 - 5% in the general population and the prevalence is higher in women, in smokers, and in those with a lower socio- economic status (23,24).

Table 45.3 Definitions of acute and chronic rhinosinusitis.

Type of sinusitis	Definition
Acute	Up to 4 weeks of purulent nasal drainage accompanied by nasal obstruction, facial pain/pressure/fullness, or both
Chronic	Twelve weeks or longer of two or more of the following signs or symptoms: • mucopurulent drainage • nasal obstruction • facial pain-pressure-fullness or • decreased sense of smell AND one or more of the following: • purulent mucous or oedema in the middle meatus or the ethmoid regions • polyps in the nasal cavity or middle meatus • radiological evidence showing inflammation of the paranasal sinuses

Adapted from *Otolaryngology—Head and Neck Surgery*, 137, Rosenfeld RM, Andes D, Bhattacharyya N, et al. Clinical practice guideline: adult sinusitis, pp. S1–31. Copyright © 2007, © SAGE Publications.

A diagnosis of ARS is primary based on history and physical examination. Purulent nasal drainage and nasal obstruction are often self-reported by the patient, but can also be observed on direct examination of the nares with an otoscope. Facial pain, pressure, and fullness are generally located in the anterior face and periorbital regions, but could be generalized throughout the head. Persistence of these symptoms for > 10 days or an improvement in symptoms followed by a worsening increases the likelihood of a bacterial rhinosinusitis as opposed to a viral rhinosinusitis (21). Sinus radiography is not generally indicated for diagnostic purposes as viral rhinosinusitis cannot be distinguished from bacterial rhinosinusitis in the early stages of an upper respiratory infection.

A diagnosis of CRS is more challenging and often requires the previously mentioned clinical symptoms, as well as radiological studies and/or direct visualization of the nares, to establish a diagnosis (19). A computed tomography (CT) scan of the sinuses would be the radiographic procedure of choice and typically shows opacification, air fluid levels, or moderate-to-severe mucosal thickening of the sinuses. Purulent drainage, oedema of the middle meatus or ethmoid region, and nasal polyps could be visualized by nasal endoscopy.

The pathophysiology of rhinosinusitis is complex and probably involves anatomical, inflammatory, and infectious mechanisms (25). Anatomical variations of the nose, such as enlarged middle and inferior turbinates, concha bullosa, and septal deviation, could block drainage of the sinuses and predispose to bacterial overgrowth. Co-existing allergic rhinitis could lead to an inflammatory reaction within the nasal mucosa that could obstruct the sinus ostia and produce mucosal thickening, which is commonly encountered with rhinosinusitis. However, the hallmark of rhinosinusitis is a bacterial infection of the sinuses. The most common bacteria involved in ARS are *Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*, while *Staphylococcus aureus*, coagulase-negative staphylococci, and anaerobes predominate in CRS (25,26).

The mainstay of treatment for ARS is antibiotics for 10 days, but a 3–5-day course has been shown to be as effective in some studies (27,28). Most guideline statements recommend amoxicillin as the first-line antibiotic, followed by a macrolide antibiotic (e.g. clarithromycin, azithromycin) or trimethoprim-sulfamethoxazole (19). Treatment with intranasal steroids, oral/topical decongestants, and nasal saline irrigation may also reduce symptom scores in those with ARS (29–32).

Recent guideline statements recommend that antibiotics only be used in patients with CRS that have purulent nasal drainage (19). Several studies have demonstrated that 2–6-week courses of antibiotics are effective in the treatment of CRS (33,34). Fluoroquinolones (e.g. ciprofloxacin), macrolides, and amoxicillin/clavulanic acid are the antibiotics of choice to treat CRS. If patients have nasal polyps or co-existing atopy then intranasal corticosteroids and leukotriene antagonists (e.g. montelukast) may also improve symptomatology (35). Endoscopic sinus surgery is reserved for patients that are refractory to medical therapy and have continued endoscopic and/or radiographic evidence of obstruction of the sinus ostia that predisposes them to recurrent bouts of rhinosinusitis.

Headache and facial pain are common complaints in patients diagnosed with CRS. Ling and Kountakis (36) interviewed 210 consecutive patients with CRS undergoing endoscopic sinus surgery and reported that 78% experienced facial pain/pressure and

71% had headaches. Banerji et al. (37) compared the prevalence of CRS symptoms in those with and without nasal polyps and found that headache/facial pain was more common in those without nasal polyps (95% vs 83%; $P = 0.02$), but nasal obstruction and anosmia were more common in those with nasal polyps. Another study (38) demonstrated that 29% of patients with purulent drainage on nasal endoscopy experienced facial pain. The differences in the prevalence rates noted in these studies might be partially explained by use of different outcome measures to define facial pain (e.g. sinus pressure vs sinus/facial pain vs headache). For example, some patients may not perceive 'sinus pressure' or 'sinus/facial pain' as headache as the pain is localized to the face.

Other studies have reported the locations of rhinosinusitis and facial pain may not always be congruent. Clifton and Jones (38) defined rhinosinusitis as the presence of purulent drainage on nasal endoscopy and found that only 65% of the time did the location of the sinusitis correspond to that of the facial pain. Another study (39) reported no correlation between the site of sinus pain and the radiographic location of sinusitis, but they included a number of abnormalities on imaging that would be unlikely to produce pain (e.g. mucosal thickening and mucus retention cysts).

A recent study (40) showed that CRS may also be associated with the prevalence of chronic daily headache (≥ 15 days per month with headache). It was reported that the risk of chronic daily headache was increased ninefold in those with CRS versus the general population (40). The characteristics of the headaches associated with CRS included a bilateral location, mild-to-moderate intensity, and an absence of migraine-associated symptoms. These results suggest that CRS may be associated with frequent headaches that resemble chronic tension-type headache.

Evidence suggests that medical and surgical treatments of CRS may improve headache and/or facial pain. Zeng et al. (41) randomized patients with CRS to either an antibiotic (clarithromycin) or nasal steroid (mometasone furoate) and found that both therapies reduced scores of headache versus baseline after 12 weeks of treatment. Lal et al. (42) studied 211 patients referred to an otolaryngology clinic for complaints of sinus pressure, pain, or headache and reported that medical and/or surgical otolaryngic therapies improved pain in 52% of referred patients. A recent meta-analysis (43) included the results of 21 studies of endoscopic sinus surgery in the treatment of CRS. The pooled analyses showed that both headache and facial pain were significantly reduced postoperatively compared with their pre-operative values, but the effect sizes were considered moderate for facial pain and small for headache. It should be noted that the outcome measures used in these studies were visual analogue scales and symptoms scores were obtained from questionnaires administered pre- and postoperatively. None of the studies used headache diaries to document the frequency of headache that was experienced both prior to and after the surgical intervention.

Chronic rhinitis

Chronic rhinitis is a disorder of the nose associated with rhinorrhoea, nasal congestion, postnasal drip, nasal itchiness, and sneezing. Symptoms of rhinitis can be perennial, seasonal, or both. Chronic rhinitis can be further categorized into allergic (AR), nonallergic (NAR), and mixed rhinitis (MR) subtypes. A diagnosis of AR requires the presence of rhinitis symptoms upon exposure to an allergen, positive allergy testing to that allergen, and a lack of rhinitis symptoms upon exposure to non-allergic rhinitis triggers (e.g. cigarette smoking, perfumes, gasoline, etc.). Patients with NAR experience rhinitis symptoms to non-allergic triggers and have negative allergy testing to allergens that are indigenous to their area. Patients with MR have rhinitis symptoms to both allergic and non-allergic triggers.

The prevalence of chronic rhinitis in the general population ranges from 24% to 54% (44–47). Of those with chronic rhinitis, AR accounts for 43%, while NAR and MR occur in 23% and 34%, respectively (48). Immunological mechanisms are important in those with allergic rhinitis subtypes (e.g. AR, MR) and involve the binding of allergens to IgE antibodies that are bound to the surface of mast cells, which results in their degranulation (49). Neurological mechanisms predominate in those with non-allergic subtypes (e.g. NAR, MR) and include an upregulation of nerve growth factor, substance P, and voltage-gated sodium channels within neurons found in nasal turbinate biopsies of patients with rhinitis patients (50–52).

The treatment of chronic rhinitis depends upon the rhinitis subtype that is diagnosed in the patient. Patients with AR or MR may benefit from oral and nasal antihistamines, nasal steroids, anticholinergics, or antileukotriene drugs (53,54). Oral or subcutaneous immunotherapy (e.g. allergy shots) can also be used if pharmacotherapy fails to control symptoms (53). Patients with NAR are generally treated with intranasal steroids and intranasal antihistamines (53,55–57).

AR and hay fever (a term used to designate AR) have been associated with an increased prevalence of migraine headache in past studies. Ku et al. (58) found that the prevalence of migraine was 34% in patients with AR and 2% in controls ($P < 0.05$). Meltzer et al. (59) conducted a telephone survey of patients with AR in Latin America and reported that 41% experienced migraine headache. Several other studies demonstrated that migraine was 1.5–2.9 times more common in those with hay fever (60–62).

More recent studies suggest that patients with chronic rhinitis may have a more severe clinical phenotype of migraine than those without rhinitis. Martin et al. (63) found that migraine headache frequency and headache-related disability were increased by 34% and 33%, respectively, in migraineurs as compared to those without chronic rhinitis. A second clinic-based study (64) also demonstrated similar increases in headache frequency and headache-related disability in patients with chronic rhinitis, but also reported that those with the MR and NAR subtypes had greater effect sizes for these outcomes measures than patients with the AR subtype. Therefore, it appears that patients with non-allergic rhinitis triggers may have the highest migraine frequency and disability.

Medical treatments for rhinitis have been associated with a decreased frequency and severity of headache and sinus pain/pressure in selected studies. The administration of subcutaneous immunotherapy was associated with a 52% decrease in migraine frequency and 45% reduction in headache-related disability in younger migraineurs with allergic rhinitis (65). Intranasal fluticasone, which is a corticosteroid, led to significantly greater relief from sinus pain and pressure than placebo in patients with AR (66). Another study found a 65% decrease in headache severity in patients with non-allergic rhinitis treated with capsaicin nasal spray versus placebo (67).

Vacuum headaches, infraorbital nerve dehiscence, and airplane headache

'Vacuum headaches' were popularized by Sluder (68) and described as frontal or maxillary headaches that occurred as a consequence of

negative pressure changes within the sinuses due to air flow obstruction at the ostia of the sinuses. In fact, studies have demonstrated that negative pressures develop when the size of the ostia is reduced below a certain threshold (69). These negative pressures are thought to occur as a result of gas absorption in a closed sinus and ciliary function that propels mucous out of the sinus creating a piston effect (70,71). The exact mechanisms through which negative pressure might produce pain are unknown, but one investigator found that hyperaemia was associated with the positional discomfort that resulted after occlusion of the maxillary sinus (72).

Dehiscence of the infraorbital nerve has been implicated as a possible cause of vacuum headaches of the maxillary sinus (73). Normally, the infraorbital nerve is surrounded by a bony canal in the roof of the maxillary sinus prior to its exit from the infraorbital foramen. Autopsy series suggest that 12–16% of cadavers have complete dehiscence of the infraorbital nerve. Whittet (73) reported that six of 12 patients with infraorbital nerve dehiscence presented with atypical facial pain. He further postulated that the pain was caused by exposure of the infraorbital nerve to the negative pressures encountered within the maxillary sinus as a result of small ostia.

Airplane headache is a type of the headache that occurs with air travel that is thought to be caused by pressure changes within the sinuses (see also Chapter 56) (74). Most of the cases occur upon descent of the aircraft, but some may be precipitated by ascent. It is theorized that expansion of gases during ascent and negative pressures created during descent produce barotrauma to the sinuses (75). The headaches are generally unilateral, severe, and located in the frontoorbital location in 76% (74). Their duration is less than 30 minutes. Treatment with topical/oral decongestants and triptans has been reported to prevent these headaches (76).

Mucosal contact points

Mucosal contact points can occur between various structures in the nares. They generally develop in patients with anatomical variations such as a deviated nasal septum, pneumatized or paradoxically bent turbinates, or enlargements of the bony structures within the nose (e.g. concha bullosa, uncinate process, or halar nasal cells). These contact points are theorized to activate the trigeminal afferents within the nasal cavity, producing headache and facial pain. Although anatomical variations within the nose/sinuses have been associated with headache and facial pain, these variations occur in similar proportions in symptomatic and asymptomatic people (77). Therefore, the presence of head pain and any anatomical abnormality of the nose/sinuses does not establish a causal relationship.

Several case series have reported that surgical correction of mucosal contact points can ameliorate headache disorders (78–83). Yazici et al. (83) studied 73 patients with primary headache disorders that had anatomical variants of the nasal septum and turbinates. Seventy-three per cent (n = 53) of this group did not respond to medical treatment of their headache disorder and were later offered surgical correction of their anatomical variant. Compared to baseline, those receiving surgery (n = 38) had a significant reduction in their visual analogue scale score for headache at 3–6 months after surgery, while those refusing surgery showed no change from baseline. Behin et al. (84) reported their results of patients with refractory migraine (n = 12; 57.2%) or transformed migraine (n = 9; –42.8%) that had radiographic evidence of contact points in the sinonasal area and who underwent endoscopic sinus surgery and septoplasty. Headache frequency and headache-related disability decreased by 57% and 68%, respectively, in these patients 6–62 months after the surgical procedure. Welge-Luessen et al. (81) reported on 20 patients with headache and endonasal mucosal contact points. The diagnoses in these patients included migraine and cluster headache. Following septoplasty, with or without sinus surgery or middle turbinectomy, 65% experienced headache relief after a 10-year follow-up.

Application of topical lidocaine to the nasal mucosa has been used to determine the functional significance of mucosal contact points. Mokbel et al. (80) studied 120 patients undergoing endoscopic surgery and classified them as responders or non-responders based on the relief of facial pain by application of topical lidocaine. Ninety-nine per cent of responders improved from surgery versus 40% in the non-responder group. The authors suggested that a lidocaine test may be used as a diagnostic tool to predict success of endoscopic surgery.

Evidence contrary to the 'mucosal contact theory' is the fact that the prevalence of nasal mucosal contact points is similar in those with and without facial pain (4% in both groups) (85). One has to also consider that there is a tendency for regression to the mean in clinical studies involving headache and that the aforementioned studies were not placebo controlled. Other factors, such as analgesic overuse and psychological issues, were not adjusted for in these studies, which could significantly affect headache outcome measures.

The possibility exists that mucosal contact points may only cause facial pain or headache in patients with primary headache disorders. Such patients may have hyperactivity of the trigeminal system and further activation of trigeminal afferents by a mucosal contact point might be enough to trigger a headache.

Taken together, data indicate that selected patients with headache may be due to nasal/sinus anatomical non-inflammatory abnormalities. The attending physician should consider a possible nasal origin in the case of nasal, frontal, and/or periorbital headaches that are refractory to usual care and probably atypical, as compared to usual primary headaches. Under these circumstances, appropriate CT scans and direct endoscopic examinations are advisable. Surgical procedures may be planned if anatomical changes are found and local anaesthesia proves to be positive, but decisions will always have to be taken based on careful individual analyses, including a headache diary, as this relationship remains highly controversial.

Mid-segment facial pain

Mid-segment facial pain, considered the most frequent pain syndrome in a rhinology clinic (85,86), has been described as a sensation of pressure or tightness over the middle third of the face that would resemble tension-type headache in all aspects except for its location. There is no nausea, vomiting, photophobia, or phonophobia. As no abnormalities are detected with nasal endoscopy and on a CT scan of the paranasal sinuses, mid-segment facial pain most likely has the same underlying mechanisms as tension-type headache, which is postulated to involve a central dysmodulation of pain transmission (87). So far, there is not enough evidence to support this entity as an independent disorder.

Potential mechanisms

There are several potential mechanisms through which sinus and nasal disorders could be associated with headache, sinus pressure/discomfort, and facial pain (Figure 45.1). Firstly, these disorders could directly activate V1 and V2 afferents in the nose and paranasal sinuses to produce head pain. This could occur as a result of mucosal contact points in the nares, negative pressure phenomenon in the sinuses, release of inflammatory mediators from mast cells (if atopy is present), or cytokine release from inflammatory cells (if sinusitis is present). Secondly, disorders of the nares cause nasal congestion and/or obstruction that might disrupt sleep or lead to obstructive sleep apnoea, which could precipitate headaches (88–90). In addition, they can produce snoring, which has been associated with chronic daily headache (91). Thirdly, they might not directly trigger headache or facial pain, but could be associated with other disorders that may cause or modulate headache disorders. For example, chronic rhinitis is more common in those with depression, obstructive sleep apnoea, and asthma, which are associated with the prevalence and attack frequency of migraine (62,92–94). Fourthly, there could be shared environmental or genetic factors that might explain the association. For example, rhinitis is more prevalent in those that smoke and smoking is associated with a greater attack frequency of migraine (95,96). Finally, it is possible that this is a spurious association and all of the 'sinus symptoms' represent cranial autonomic symptoms that occur as part of a migraine attack (8).

Differential diagnosis

There are a number of headache disorders that might be confused with headaches attributed to the nasal mucosa, septum, turbinates, and rhinosinusitis (97). Firstly, migraine, the trigeminal autonomic cephalalgias (cluster, episodic/chronic paroxysmal hemicranias, short-lasting, unilateral, neuralgiform headaches with conjunctival injection and tearing (SUNCT/SUNA), hemicrania continua) often have cranial autonomic symptoms and thus could mimic many of the symptoms encountered with rhinological headaches (see also Chapter 17). However, each of these headache types have characteristic features that can differentiate them from rhinological headaches (98). These include stereotyped circadian rhythms, such as in cluster headache, short-lasting episodes, such as in SUNCT or absolute indomethacin effect, such as in hemicrania continua. Secondly, mid-segment facial pain and headaches attributed to chronic rhinosinusitis have been reported to have characteristics of chronic TTH (see also Chapter 29). It is interesting to postulate that subgroups of patients with a TTH-like pain could have a rhinologic aetiology for their headaches. Thirdly, trigeminal neuralgia is characterized by short-lived bursts of facial pain lasting from seconds to minutes that are located mostly in the maxillary and mandibular regions and is distinguished from rhinogenic headaches by its short duration (see also Chapter 27). Finally, the headaches in the so-called 'salt and pepper in the face syndrome' are located in the orbital region and may indicate an evolving brainstem stroke (99,100). These headaches are differentiated from disorders of the nose and sinuses by their associated neurological signs and symptoms.

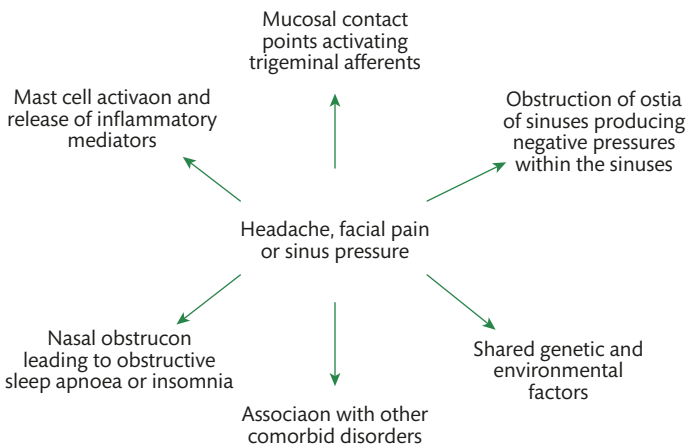
Mucosal contact points activating trigeminal afferents
Mast cell activaon and release of inflammatory mediators
Obstruction of ostia of sinuses producing negative pressures within the sinuses
Headache, facial pain or sinus pressure
Nasal obstrucon leading to obstructive sleep apnoea or insomnia
Shared genetic and environmental factors
Associaon with other comorbid disorders

Figure 45.1 Potential mechanisms through which nasal and sinus disorders could produce headache, facial pain, or sinus pressure.

Clinical approach

One must develop a clinical approach to the management of nasal and sinus disorders in headache patients to avoid unnecessary diagnostic testing, medical treatments, and surgeries. Rhinitis, rhinosinusitis, and anatomical abnormalities of the nose/sinuses are common disorders and clearly will be encountered in patients with primary headache disorders. The question remains as to whether they play a causative role for headaches or are simply innocent bystanders. Given that the data are inconclusive, the authors recommend medical treatment of rhinitis and rhinosinusitis in headache patients. The medical therapies are listed in Table 45.4, and

Table 45.4 Medical therapies used to treat specific nasal and sinus disorders.

Nasal and sinus disorders	Medical therapies
Acute rhinosinusitis	• First-line antibiotics: amoxicillin • Second-line antibiotics: macrolide or trimethoprim-sulfamethoxazole • Use of nasal steroids may shorten the duration of symptoms • Oral/intranasal decongestants may improve congestion (short-term use advised)
Chronic rhinosinusitis	• Antibiotics: fluroquinolone, macrolide, or amoxicillin/clavulanic acid • Intranasal steroids indicated • Saline lavage helpful
Nasal polyps	• Intranasal/oral steroid • Antileukotriene medications
Allergic and mixed rhinitis	• First-line: oral antihistamine, intranasal steroid • Second-line: antileukotriene medications • Moderate-to-severe disease: immunotherapy (allergy shots)
Nonallergic rhinitis	• Intranasal steroids, intranasal antihistamine • Oral antihistamines do not work
Deviated septum/ obstruction of maxillary ostia	• Oral/intranasal decongestants • Nasal steroids if allergies present

differ depending upon which nasal and sinus disorder that is being treated. These therapies generally have a low side effect profile and their use will improve symptoms related to the nasal and sinus disorders, and could improve headache and sinus pressure/discomfort in some instances. The authors would discourage the use of surgical interventions for the sole purpose of treating headache, as the data do not currently support such an approach.

Conclusion

'Sinus headaches' encompass a variety of nasal and sinus disorders that have been associated with an increased prevalence of headache disorders. Emerging data suggest that treatment of these disorders might reduce sinus pain/pressure, as well as headache in some instances. It is unknown if the nasal or sinus disorders cause headache or if their symptoms are simply a result of an underlying primary headache secondary to activation of cranial parasympathetics. Clearly, further research is indicated to elucidate the complex relationship between these disorders and headache.

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46

Giant cell arteritis and primary central nervous system vasculitis as causes of headache

Mamoru Shibata, Norihiro Suzuki, and Gene Hunder

Giant cell arteritis

Introduction

Giant cell arteritis (GCA) is a granulomatous vasculitis affecting large- and medium-sized blood vessels, especially the proximal aorta and its branches. There is a predilection for extracranial branches of the carotid arteries, including the superficial temporal artery. As such, this disorder is also referred to as temporal arteritis. Clinical manifestations are caused by inflammation and ischaemia. When a new headache has developed in a patient over the age of 50 years physicians should always be alert to the possibility of GCA. The headache is often unilateral but may be more generalized. Inspection and palpation of the scalp arteries, particularly the temporal artery ipsilateral to the headache is essential when evaluating suspected cases. Ultrasonography over the affected temporal artery should be performed, which is helpful in determining the appropriate site of biopsy. High-dose corticosteroids are the mainstay of treatment. Steroid administration does not have to wait until the temporal artery is biopsied. The aim of early therapy is to prevent visual loss and other vascular complications.

Epidemiology

The disease primarily affects people over 50 years of age (1). The female-to-male ratio is approximately 2–3:1 (1). The incidence is higher in certain ethnic groups. Most patients with GCA are white. Scandinavians and North Americans of Scandinavian origin have the highest incidence rates (> 17 per 100,000 individuals aged > 50 years), whereas Southern Europeans have incidence rates of < 12 per 100,000 individuals aged > 50 years. In one study the incidence of GCA in black individuals was one-seventh that of white persons (2). Similarly, a review of US patients with biopsy-proven GCA found a lower prevalence in Asian than in white patients (3). The incidence in Japanese people is even lower. A Japanese government-supported survey revealed that the prevalence in patients aged > 50 years was 1.47 per 100,000 population in Japan (4).

It is well-known that GCA is often found in patients with polymyalgia rheumatica (PMR). The association with PMR is apparently influenced by ethnicity, as shown by a lower rate (30.3%) in Japanese patients with GCA (4).

Pathology and pathogenesis

Inflammatory changes chiefly involve the large- and medium-sized muscular arteries, especially the proximal aorta and its branches (5,6), which have a prominent internal elastic membrane and vasa vasora. Because these structures are less developed in intracranial arteries, they are rarely affected by GCA (7). The final pathological picture of GCA is panarteritis, which involves all vascular layers. The classic pathological hallmarks consist of a granulomatous inflammatory infiltrate with lymphocytes, macrophages, and multinucleated giant cells, which are usually observed at the intima–media junction (Figure 46.1). Such inflammatory changes within the arterial walls are often seen in a segmental fashion, which necessitates sampling of long segments in the diagnostic biopsy. Jaw claudication and diplopia are the symptoms with significant predictive value for positive biopsy, with likelihood ratios of 4.2 and 3.4, respectively (8).

The cause of GCA remains elusive. Non-genetic factors also seem to be concerned with the aetiology. Several studies have explored the involvement of infectious agents with inconsistent results (9). With regard to cardiovascular risk factors, an increased risk of GCA in heavy smokers, and in individuals with previous atherosclerotic disease has been reported (10). In patients with GCA, the most commonly identified genetic association is with the HLA-DRB1*0401 allele (11). Scores of susceptible genetic foci, most of which are related to immune response and inflammation, have been reported. These findings strongly raise the possibility that immunogenicity determined by a genetic factor(s) plays a role in the development of disease.

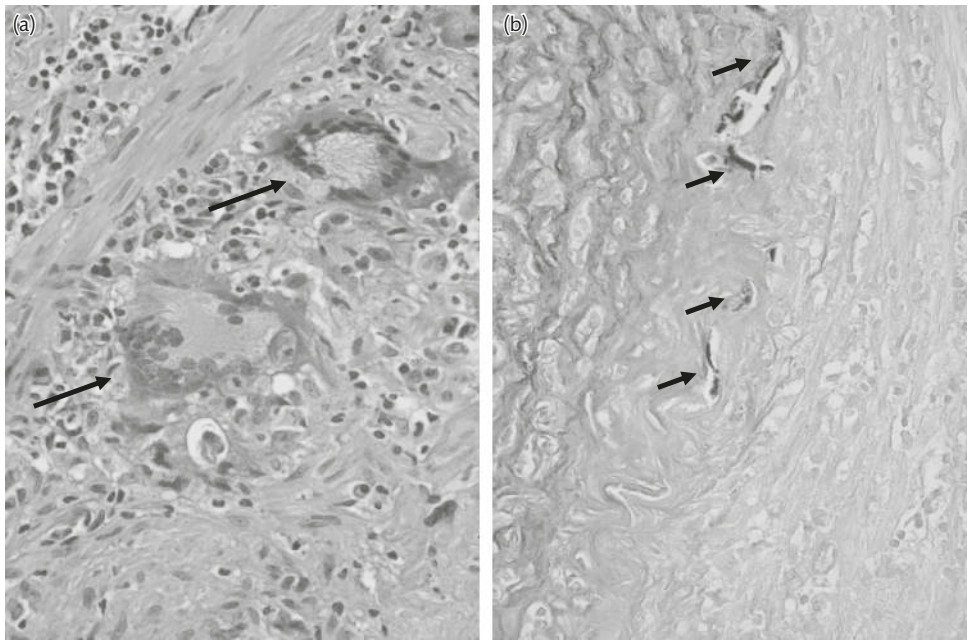

Figure 46.1 Pathological findings of the temporal artery biopsied from an 86-year-old man with giant cell arteritis.

(A) The arterial wall is infiltrated by numerous mononuclear cells. Multinucleated giant cells are observed in the intima–medial border zone (arrows). Magnification: 400×, haematoxylin and eosin staining. (B) The continuity of the internal elastic lamina is lost (arrows), which is consistent with the destruction of the internal elastic lamina. Magnification: 400×, elastic van Gieson staining.

Courtesy of Dr Noboru Imai at Department of Neurology, Japanese Red Cross Shizuoka Hospital.

As for the inflammatory mechanisms underlying GCA, evidence shows that dendritic cells located at the adventitia–media border of the artery are crucial in initiation of the vasculitic process (Figure 46.2) (12). Dendritic cells serve as arterial wall sentinels in the resting state. They can be activated by Toll-like receptor (TLR) ligands, which might be microbial antigens or unknown autoantigens. Intriguingly, Pryshchep et al. (13) demonstrated that human medium and large arteries display site-specific patterns of TLR expression. Quantitative reverse transcription polymerase chain reactions have shown that the temporal and subclavian arteries express higher transcripts for TLR2 and TLR8 as compared to other vessels, whereas TLR3 expression is lacking in these arteries. Such distinct expression patterns may explain the tropism of GCA-associated inflammatory processes. The activated dendritic cells become chemokine-producing effector cells, which recruit CD4 T cells and macrophages into the vascular wall through the vasa vasorum. The activated dendritic cells provide the necessary costimulatory signals to trigger T-cell activation. The recruited and activated $CD4^+$ T cells in the artery wall undergo clonal proliferation and begin to release cytokines, including interferon (IFN)-γ, and interleukin (IL)-12. IFN-γ-producing T cells seem to be important for the formation of GCA-associated pathological changes, because they are not seen in the vessels in patients with PMR (14). In addition to such type 1 helper T cells (T_H1), IL-17-producing type 17 helper T cells (T_H17) are also activated. Many vascular cell types, including smooth muscle and endothelial, are stimulated by IL-17. The IL-17-induced inflammatory changes are known to be active in the acute phase of GCA. Meanwhile, T_H1-mediated processes are prolonged, such that GCA transforms into a pure T_H1 disease in the chronic phase. T-cell subsets were explored in the peripheral blood in patients with GCA. Among $CD4^+$ T cells, the proportion of circulating T_H1 and T_H17 cells was 20.6% and 2.2% on average, respectively, in untreated patients with GCA versus 11.8% and < 0.59%, respectively, in healthy controls (15). The produced cytokines play a pivotal role in regulation of the differentiation and function of macrophages, which are directly related to arterial wall damage. In the adventitia, macrophages secrete inflammatory cytokines, such as IL-1β, tumour necrosis factor (TNF)-α and IL-6, whereas in the media they release metalloproteinases (MMPs) and reactive oxygen species. Hernández-Rodriguez et al. (16) demonstrated that patients with corticosteroid-resistant patients with a strong systemic inflammatory response had elevated tissue expression of IL-1β, TNF-α, and IL-6. Of note, high production of TNF-α was associated with longer corticosteroid requirements. MMP-9 and MMP-2 can cause the fragmentation of internal elastic lamina with their elastinolytic properties. Under the circumstances, repair mechanisms driven by growth factors become aberrant. In particular, platelet-derived growth factor (PDGF) appears to contribute to luminal occlusion via excess intimal hyperplasia (17). PDGF also promotes the migration of vascular smooth muscle cells from the media to the intima (18). In GCA, dendritic cells in the lesions possess the chemokine receptor, C-C chemokine receptor type 7 (CCR7). Locally synthesized chemokines, such as chemokine (C-C motif) ligand (CCL)19 and CCL21, bind to CCR7 to trap the dendritic cells within the arterial walls, thus perpetuating the aforementioned inflammatory cascade, culminating in the alterations of vascular structure and resultant tissue ischaemia (19). As mentioned earlier, smoking and atherosclerosis are known to be risk factors for GCA. It is deduced that these conditions worsen the pathological processes by promoting inflammation. Besides these

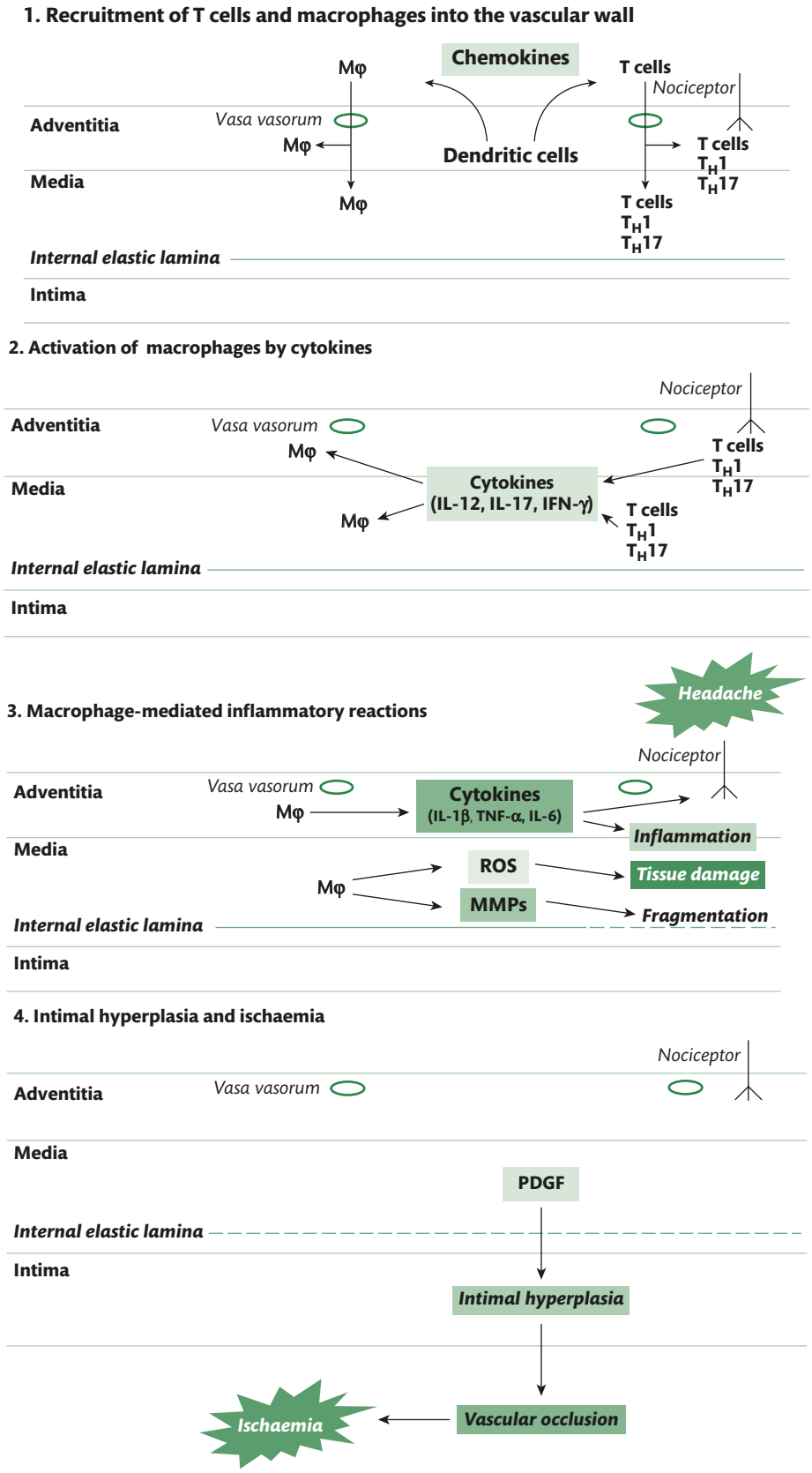

Figure 46.2 Schematic representation of giant cell arteritis-associated disease processes.

(1) T cells and macrophages (Mϕ) are recruited through the vasa vasorum by the actions of chemokines secreted by dendritic cells located in the adventitia–media border. (2) Mϕ are active by cytokines synthesized by invading T cells. (3) Mϕ secrete pro-inflammatory cytokines, such as interleukin (IL)-1β, tumour necrosis factor (TNF)-α, and IL-6. Adventitial nociceptors are stimulated, and headache is induced by pain signal transmitted to the trigeminocervical complex. The pro-inflammatory cytokines amplify inflammatory reactions in the vascular wall. Mϕ-produced reactive oxygen species (ROS) cause tissue damage. Matrix metalloproteinases (MMPs) contribute to the fragmentation of internal elastic lamina with their elastinolytic properties. (4) Platelet-derived growth factor (PDGF) induces intimal hyperplasia, which leads to vascular obstruction. Tissue ischaemia ensues. These processes can co-exist at identical time points.

Table 46.1 Common clinical manifestations associated with giant cell arteritis and primary central nervous system vasculitis

Giant cell arteritis		Primary central nervous system vasculitis	
Headache	66%	Headache	64%
Scalp tenderness	50%	Altered cognition	50%
Jaw claudication	50%	Hemiparesis	44%
Fever, fatigue, weight loss	50%	Persistent neurological deficits/stroke	40%
Polymyalgia rheumatica	40%	Aphasia	28%
Visual impairment	20%	Transient ischemic attack	28%
Peripheral neuropathy	14%	Nausea/vomiting	25%
Arm claudication	10%	Visual field defect	21%
Amaurosis fugax	10%	Ataxia	19%
Respiratory symptoms	10%	Diplopia	16%
Transient ischemic attack/cerebral infarction	3%	Dysarthria	15%

Source data from: *New England Journal of Medicine*, 347, 4, Salvarani C, Cantini F, Boiardi L, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis, pp. 261-271, 2002, Massachusetts Medical Society; *The Lancet*, 380, 9843, Salvarani C, Brown RD, Hunder GG. Adult primary central nervous system vasculitis, pp. 767–777. 2001, Elsevier.

local effects, the produced cytokines contribute to systemic manifestations, such as fever and malaise.

Clinical manifestations

Common clinical manifestations associated with GCA and primary central nervous system vasculitis (PCNSV) are presented in Table 46.1. A new-onset headache is the most frequent symptom, occurring in two-thirds of patients (20). According to ICHD-3B, GCA-induced headache is coded as '6.4.1. Headache attributed to giant cell arteritis' (Box 46.1). Head pain typically lies over the temporal or occipital areas, but it may localize to any part of the head. Pain is usually of sudden onset, and its intensity is moderate or severe in more than half of cases. Thunderclap headache has been also reported but is uncommon (see also Chapter 34) (21). Pain is usually continuous throughout the day, often interferes with sleep, and is characterized by poor response to standard analgesics. Patients with such headache most likely complain of scalp tenderness. In rare cases, headache may mimic features of migraine or trigeminal autonomic cephalalgias (22,23).

Box 46.1 ICHD-3 criteria for '6.4.1 Headache attributed to giant cell arteritis'

- **A** Any new headache fulfilling criterion C.
- **B** Giant cell arteritis (GCA) has been diagnosed.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in close temporal relation to other symptoms and/or clinical or biological signs of onset of GCA, or has led to the diagnosis of GCA
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with worsening of GCA
    - (b) Headache has significantly improved or resolved within 3 days of high-dose steroid treatment
  - **3** Headache is associated with scalp tenderness and/or jaw claudication.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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Nearly half of patients present with jaw claudication due to ischaemia of the muscles of mastication. Jaw claudication is a high predictor of GCA but is not necessarily pathognomonic (24). At times, intermittent claudication can affect the arms, tongu,e or pharyngeal muscles.

Systemic manifestations, including fever, anorexia, and malaise, are common. Fever is usually low grade, but it sometimes rises up to 39–40°C in about 15% of patients and might be the only presenting symptom (25). Weight loss can be seen. Cough may be present, possibly owing to ischaemia of the cough receptor (26).

On physical examination, the frontal or parietal branches of the superficial temporal arteries may be tendered, nodular, and thickened (Figure 46.3). Reflecting the compromised blood flow, pulses may be weak or absent.

Permanent partial or complete loss of vision in one or both eyes occurs in as many as 20% of patients, often in the early disease stage, a devastating outcome that must be avoided (27). Visual loss results from arteritic anterior ischaemic optic neuropathy (AAION), which is caused most commonly by narrowing or occlusion of the posterior ciliary arteries. Less commonly, retinal artery occlusion is responsible for visual loss. The ocular symptom is painless. The early fundoscopic findings in anterior ischaemic optic neuropathy consist of slight pallor and oedema of the optic disc, with scattered cotton-wool spots and small haemorrhages, followed by the development of optic atrophy. Unless treated, the second eye is likely to become affected within 1–2 weeks. Once visual impairment is established, it is usually permanent. Amaurosis fugax is reported in 10–15% of patients, and can precede permanent visual loss. An Italian study reported visual symptoms in 30.1% of their patients, with partial or total visual loss in 19.1% (28). In their study, 92.3% were due to anterior ischaemic optic neuritis and 7.7% had central retinal artery occlusion. Visual loss was unilateral in 73.1% patients and bilateral in 26.9%. Most of them (n = 25/26) developed visual loss before the institution of corticosteroids. Of particular relevance is the lower incidence of ocular symptoms in a series of Japanese patients. Imai et al. (29) reported that ocular manifestations were identified in only two of the 19 patients studied. No loss of vision occurred. Jaw claudication is also less frequent in Japanese patients (4,29). It is inferred

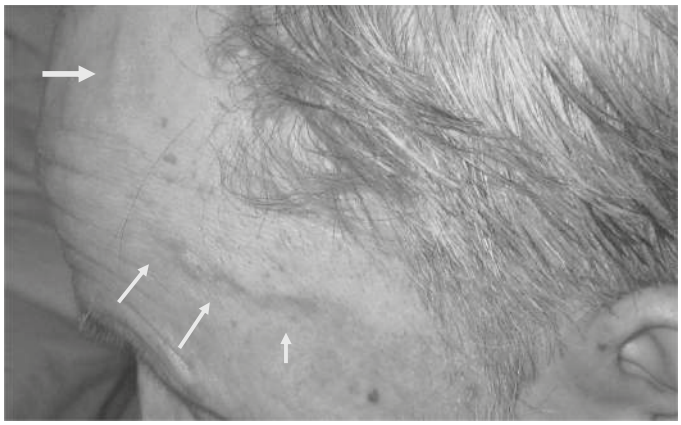

Figure 46.3 Swelling of the temporal artery affected by giant cell arteritis.

Swelling of the left temporal artery is observed (arrows).

Courtesy of Dr Noboru Imai at Department of Neurology, Japanese Red Cross Shizuoka Hospital.

that the genetic background may determine the clinical manifestations in GCA. Jaw claudication is also less frequent in Japanese patients (4,29).

Moreover, vertebrobasilar stroke, isolated choroidal ischaemia, and orbital infiltration with proptosis may occur (30,31). Transient diplopia is present in around 6% of patients. Diplopia may be due to ischaemia of extraocular muscles or cranial nerves innervating them. A case with periorbital pain and a submandibular mass has been reported (32).

Diagnostic evaluations

Blood tests

Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are usually elevated in GCA. However, normal ESR and CRP values do not exclude the diagnosis of GCA. Alkaline phosphatase and anticardiolipin antibodies can be increased in active GCA, but normalize after steroid treatment (33,34). Anaemia and thrombocytosis may occur.

Temporal artery biopsy

Temporal artery biopsy (TAB) remains the gold standard for diagnosis. As mentioned earlier, specimens of at least 1.5-2 cm long should be taken, to avoid false-negative results (35). False-negative results are attributable to sampling of a vessel segment devoid of inflammation. The length of steroid therapy seems to be critical: TAB was positive in 78% of patients treated for < 2 weeks, in 65% of those treated for 2–4 weeks; and only in 40% of those treated for > 4 weeks (36). Negative TAB findings are more common (42% of cases) in patients with clinically overt large-vessel GCA (37). Bilateral TAB may help make the diagnosis in some instances, but it does not significantly increase the diagnostic yield (38).

Fundoscopic examination

Fundoscopic evaluations should be performed in every patient with GCA. In patients with visual loss due to AAION, fundoscopy typically shows a 'chalky white' optic disc, indicative of optic nerve infarction induced by vasculitic processes (27). When visual loss is due to posterior ischaemic optic neuropathy, the optic disc appears initially normal, and disc pallor only develops a few weeks later. Therefore, fundoscopy is less useful in this condition.

Imaging studies

Several imaging modalities are available to investigate patients with GCA, which include colour Doppler ultrasonography, magnetic resonance angiography (MRA) and contrast-enhanced computed tomography angiography (CTA) can visualize the vascular lumen and wall of the aorta and its major branches. Early alterations caused by vasculitis include thickening of the arterial wall and the presence of mural oedema. Oedema typically appears as a hypoechoic rim surrounding the arterial lumen ('halo sign') on ultrasonography, as high-intensity signal on magnetic resonance imaging (MRI) T2 and fat-suppressed sequences, and as enhanced lesion on MRA and CTA (39). Importantly, the diagnostic yield increases if TAB is performed at vessel sites displaying the 'halo sign' on ultrasonography (40). Hence, ultrasonography should be used to determine the site of biopsy.

The halo sign in the temporal arteries has a sensitivity of 75% in some series and a specificity of 83% for diagnosis of biopsy-proven GCA and an overall sensitivity of 68% and specificity of 91% for GCA diagnosed according to the American College of Rheumatology (ACR) criteria (41). The bilateral halo sign is pathognomonic of GCA (41). Meanwhile, CT and MRI are suitable to study deep, large vessels, such as the aorta. CT studies have shown to detect aortic thickening, suggestive of aortitis, in 45–65% of patients at diagnosis (42,43). A prospective study pointed out that the diameters at the ascending and descending aorta significantly increased over time in a manner independent of detectable disease activity (44). Hence, long-term care should be taken not to overlook aortic lesions, which can lead to catastrophic consequences.

Fludeoxyglucose ([18F]-FDG) positron emission tomography (PET) can visualize metabolically active cells, including inflammatory cells invading the affected vessels. Hence, the technique is advantageous in detecting early large-vessel involvement in GCA before morphological changes become obvious (39). Semiquantitative assessment is possible with PET scans by measuring standardized [18F]-FDG uptake values, which is applicable to the monitoring of response to therapy. A recent meta-analysis showed that vessel uptake that was superior to liver uptake was considered an efficient marker for vasculitis. The meta-analysis of six selected studies (101 patients with vasculitis and 182 controls) provided the following results: sensitivity 0.80 (95% confidence interval (CI) 0.63–0.91), specificity 0.89 (95% CI 0.78–0.94), positive predictive value 0.85 (95% CI 0.62–0.95), negative predictive value 0.88 (95% CI 0.72–0.95), positive likelihood ratio 6.73 (95% CI 3.55–12.77), negative likelihood ratio 0.25 (95% CI 0.13–0.46), and accuracy 0.84 (95% CI 0.76–0.90) (45).

Angiography can disclose stenotic and aneurysmal changes of affected vessels. However, it has only a limited value in detecting early large-vessel GCA changes.

Diagnosis

GCA is diagnosed by taking a careful history and performing a thorough physical examination and subsequent temporal artery biopsy. The ACR 1990 criteria (**Box 46.2**) help classify and separate one form of vasculitis from others (46).

Box 46.2 1990 American College of Rheumatology classification criteria for giant cell arteritis

- Age at disease onset > 50 years:
  - Development of symptoms beginning at age 50 years or older.
- New headache:
  - New onset of or new type of localized pain in the head.
- Temporal artery abnormality:
  - Temporal artery tenderness to palpation or decreased pulsation, unrelated to arteriosclerosis of cervical arteries.
- Elevated erythrocyte sedimentation rate (ESR):
  - ESR > 50 mm in the first hour by the Westergren method.
- Abnormal artery biopsy:
  - Biopsy specimen with artery showing vasculitis characterized by a predominance of mononuclear cell infiltration or granulomatous inflammation, usually with multinucleated giant cells

For the purposes of classification, at least three criteria must be fulfilled.

Sensitivity: 93.5%; specificity: 91.2%.

Adapted from *Annals of the Rheumatic Diseases*, 71, Prieto-Gonzalez S, Arguis P, Garcia-Martinez A, et al. Large vessel involvement in biopsy-proven giant cell arteritis: prospective study in 40 newly diagnosed patients using CT angiography, pp. 1170–1176. Copyright © 2012, BMJ Publishing Group Ltd and the European League Against Rheumatism.

Management

Glucocorticoids

The majority of patients with GCA can be managed with prednisone or prednisolone. The European League Against Rheumatism (EULAR) advises that prompt treatment with a high dose of prednisolone (1 mg/kg daily) be initiated and continued for 1 month (47). The British Society for Rheumatism (BSR) recommends prednisolone 40–60 mg daily without visual loss until the resolution of symptoms and laboratory abnormalities (48). In patients at greater risk of developing visual loss, 500 mg–1 g intravenous (IV) methylprednisolone should be considered. Once visual loss has fully developed, glucocorticoids seldom reverse the devastating situation (40). IV steroid pulse therapy has not been shown to be superior to oral glucocorticoids with respect to the reduction of glucocorticoid intake and prophylaxis of ischaemic complications (49). However, initial IV glucocorticoid pulses have been shown to allow more rapid tapering of oral glucocorticoid and also to be associated with a higher frequency of sustained remission of disease after discontinuing treatment, plus a lower cumulative oral dose, than patients treated only with oral glucocorticoids (49). In terms of T-cell activity control, glucocorticoids exert a potent suppressive action on T_H17 over T_H1 (15).

After attaining remission, the glucocorticoid dosage should gradually be tapered. EULAR suggests that the prednisolone dose be reduced to 10–15 mg daily by 3 months (46). The BSR has released more detailed recommendations for steroid tapering (48). After treatment with high-dose glucocorticoids for 3–4 weeks, the prednisolone dosage can be reduced by 10 mg every 2 weeks to 20 mg, then by 2.5 mg every 2–4 weeks to 10 mg, and then by 1 mg every 1–2 months if no flare occurs. When flares occur, the glucocorticoid dose should be increased. Most patients can be withdrawn from glucocorticoids within 6–24 months after the onset of treatment (50). Meanwhile, some cases take a chronic-relapsing course and need long-term glucocorticoids at a low dose. Prophylaxis for osteoporosis and careful monitoring for latent infection, especially for tuberculosis, should be warranted.

Immunosuppressive agents

Immunosuppressive agents are used as adjunct therapy. The main reasons for using them include the refractoriness to glucocorticoids and steroid-sparing effects.

Methotrexate

There are three randomized controlled trials (RCTs) that studied the efficacy of methotrexate in recent-onset GCA (51–53). A meta-analysis of these studies showed that the addition of methotrexate at a mean dosage of 11.1 mg weekly to glucocorticoids decreased the risk of a first and a second relapse by 35% and 51%, respectively (54). However, the addition of methotrexate failed to reduce glucocorticoid-related adverse events. EULAR recommends methotrexate as adjunctive therapy in patients with large-vessel vasculitis (47).

Azathioprine

An RCT showed that azathioprine (2 mg/kg daily) exhibited a modest steroid-sparing effect in patients with GCA, which became statistically significant only after 1 year of treatment (55). The study population also included patients with PMR. Along with the low number of patients completing the study, the study has limited value in demonstrating the efficacy of azathioprine.

TNF inhibitors

Initially, two RCTs showed that adding infliximab to prednisone provided no major benefit over that provided by prednisone alone in patients with newly diagnosed GCA or PMR (56–58). However, a newly performed RCT comprising 20 glucocorticoid-naïve patients with PMR randomly assigned to receive 2 mg etanercept subcutaneously twice weekly or placebo for 2 weeks demonstrated that etanercept, but not placebo, decreased a composite index of disease activity by 24% (58). In a multicentre RCT of using adalimumab in newly diagnosed patients with GCA, the TNF-α blocker failed to decrease the prednisone dose or the proportion of patients who were relapse-free, as compared to placebo (59).

In patients with refractory GCA, a small RCT comparing 25 mg etanercept twice weekly with a matched placebo demonstrated that etanercept resulted in a lower cumulative prednisone intake after 12 months than placebo (60). Likewise, it was shown that TNF blockade in an open-label study reduced glucocorticoid requirements in patients with relapsing GCA (61). Collectively, TNF blockers are likely to be useful in reducing glucocorticoid requirement in relapsing GCA.

Tocilizumab

The novel humanized IL-6 receptor antibody tocilizumab (8 mg/kg monthly) has been reported to control the disease activity of steroid-resistant relapsing GCA (62). A multicentre open-label study demonstrated the efficacy of this agent in 19 of 22 patients (63). However,

the study also pointed out that the risk of infection should be borne in mind. Recently, a multicentre, randomized, double-blind, and placebo-controlled study (the GiACTA trial) has been designed to test the ability of tocilizumab to maintain disease remission in patients with GCA (64). In this 1-year trial, patients were assigned to receive subcutaneous tocilizumab (at a dose of 162 mg) weekly or every other week, combined with a 26-week prednisone taper, or placebo combined with a prednisone taper over a period of either 26 weeks or 52 weeks. It was revealed that tocilizumab was superior to placebo with regard to sustained glucocorticoid-free remission at 52 weeks (65).

Antiplatelet therapy

EULAR advises that all patients with GCA receive low-dose aspirin to maintain the patency of vessels (47). In a retrospective analysis of 85 patients, it has been shown that neither platelet count nor size nor aspirin treatment were significantly associated with the development of ischaemic complications (66). Contrary to expectations, patients treated with antiplatelet/anticoagulant therapy were significantly more likely to suffer cranial ischaemic events than those without. Hence, the therapeutic value of aspirin in GCA seems to be unsettled.

Box 46.3 ICHD-3 diagnostic criteria for '6.4.2 Headache attributed to primary angiitis of the central nervous system (PACNS)'

- **A** Any new headache fulfilling criterion C.
- **B** PACNS has been diagnosed.
- **C** Evidence of causation demonstrated by either or both of the following:
  - **1** Headache has developed in close temporal relation to other symptoms and/or clinical signs of onset of PACNS, or has led to the diagnosis of PACNS
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with worsening of PACNS
    - (b) Headache has significantly improved in parallel with improvement in PACNS resulting from steroid and/or immunosuppressive treatment.
- **D** Not better accounted for by another ICHD-3 diagnosis.[1]

Note

[1]In particular, central nervous system (CNS) infection, neoplasia, and reversible cerebral vasoconstriction syndrome have been excluded by appropriate investigations.

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Primary central nervous system vasculitis

Introduction

PCNSV, or primary angiitis of the central nervous system (PACNS), is a rare form of vasculitis of unknown cause, which affects only intracranial vessels and manifests as a constellation of neurological symptoms, including headache (67,68). In ICHD-3B, PACNS-associated headache is classified as '6.4.2. Headache attributed to primary angiitis of the central nervous system' (Box 46.3). It accounts for only 1% of the systemic vasculitides. Vasoconstrictive changes on angiography along with headache sometimes poses a diagnostic challenge in terms of distinction from reversible cerebral vasoconstriction syndrome (RCVS) (69).

Clinical manifestations

PCNSV most frequently affects middle-aged men, but both sexes and all ages many develop this condition (67,70). Headaches are recognized in approximately 60% of patients with PCNSV (70,71). Unlike GCA, PCNSV-associated headaches are indolently progressive, and may be moderate to severe. Migraine-like headache has also been reported (72). Insidious cognitive impairment is common. Strokes or persistent neurological deficits occur in 40% of cases, and transient ischaemic attacks have been reported in 30–50% of patients (67). Although PCNSV is classically regarded as a small-vessel vasculitis, clinical symptoms related to large-vessel

Table 46.2 Discriminating features of primary angiitis of the central nervous system (PACNS) and reversible cerebral vasoconstriction syndrome (RVCS)

Characteristic	PACNS	RVCS
Demographics		
Sex	Men more than women	Women more than men
Median age range (y)	40–60	20–40
Clinical symptoms		
Headache	Chronically progressive	Acuity and severity warranting evaluation for subarachnoid haemorrhage
Focal symptoms (e.g. strokes, TIAs)	Yes, but rare at onset of symptoms of headache	Yes, may occur with onset of headache
History provocative vasospastic syndromes (e.g. migraine, peripureum) or medication use	No	Yes
Dynamic improvement of angiographic abnormalities after 3 months	Variable, depending on chronicity of symptoms, as well as affected vessel size	Yes
CSF sample findings	Leukocytosis and elevated total protein level, mild to moderate	Normal
Drug treatment	Prednisone with cytotoxic agent	Calcium channel blockers

TIA, transient ischaemic attack; CSF, cerebrospinal fluid.

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disease, stroke, including aphasia (28%), and visual field deficits (21%), seem to be more common than initially envisioned (67,70). Seizures have been reported in < 25% of patients. Fever, weight loss, and night sweats are present in < 20% of patients.

Diagnostic evaluations

MRI findings are abnormal in 90–100% (67). Most commonly, lesions are identified in the subcortical white matter, followed by the deep grey matter, the deep white matter, and the cerebral cortex (73). Infarcts may be seen in approximately 50% of cases. Lesions occur bilaterally and affect the cortex, as well as the subcortex. Mass lesions, which are sometimes mistaken for malignant neoplasms, can be seen in as many as 15% of cases. Gadolinium enhancement is observed in up to one-third of cases; leptomeningeal enhancement may occur in 10–15% of cases.

Cerebrospinal fluid (CSF) analysis detects abnormalities in 80–90% of patients (74). Typically, CSF samples exhibit modest elevations in white blood cell count and total protein.

Angiographic findings consistent with PCNSV include 'beading', or multiple regions of narrowing in a given vessel, with interposed regions of dilatation or normal luminal architecture (70). Such radiological findings combined with headache can form a clinical image analogous to RCVS. However, the distinction between the two disorders is feasible with careful diagnostic analysis (Table 46.2) (69). Although PCNSV was originally considered a small-vessel vasculitis, radiological evidence that supports the involvement of larger vessels exists (70,75).

Histologically, the lesions are characterized by a granulomatous or a lymphocytic inflammatory reaction with a variable number of plasma cells, histiocytes, neutrophils, and eosinophils.

Management

Patients with definite PCNSV should be treated with prednisone (1 mg/kg daily) or the equivalent of a similar corticosteroid. Patients with severe manifestations should also be given oral cyclophosphamide (2 mg/kg daily) or pulse cyclophosphamide (76). In rapidly progressive cases, IV methylprednisolone (1 g IV daily for 3 days) should be instituted. Thereafter, the patient is given oral prednisone (1 mg/kg daily) for 1 month, and the dosage is subsequently tapered slowly over 12 months (70).

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47

Headache related to an intracranial neoplasm

Elizabeth Leroux and Catherine Maurice

Introduction

Patients presenting with headache often worry about having a brain tumour. Specific tumours may, indeed, induce headache by varied mechanisms, producing different phenotypes, and virtually all headache and facial pain phenotypes can be secondary to a brain tumour. Then, however, clinical clues to a secondary aetiology are often present. Headaches may also be related to the treatment of intracranial neoplasms such as intrathecal chemotherapy, radiotherapy, and craniotomy. The International Classification of Headache Disorders, third edition (ICHD-3) therefore includes several codes related to brain tumours (Table 47.1), illustrating this diversity. Although not specifically represented in the classification, the association of trigeminal autonomic cephalalgias (TACs) with pituitary tumours is now supported by the literature and is discussed in a specific section.

Headache related to an intracranial neoplasm

Epidemiology

Primary brain tumours are rare, representing 2% of all tumours, with a lifetime prevalence of 0.55%. The annual incidence rate is 26 per 100,000 in adults, and increases after the age of 65 years (1–3). The incidence in children is approximately 5 per 100,000 per year (2). Approximately 30% of tumours are benign, with meningioma being the most frequent subtype. In children > 4 years old, infratentorial masses are more frequent than supratentorial ones; the reverse is seen in adults (2). The precise incidence of brain metastases is unknown, but they remain the most common intracranial tumour, outnumbering primary tumours by a ratio of 10:1 (4). The prevalence of headache in patients with intracranial tumours ranges from 32% to 71%. Similarly, metastases are associated with headache in 66–77% of cases (5,6). The variation between series can be explained by the age distribution of the cohorts, recall, or selection bias, and the presence of a treatment at the moment of data collection. It has to be kept in mind that the 1-year prevalence of headache as a symptom in the general population is near 50% (7). In children, headache is also the first symptom of brain tumour in 50% of cases, except in those < 2 years old (8). The clinical picture is different in this age group. The first complaints are usually nausea, vomiting, epileptic seizures, weakness, diplopia, and loss of balance (9,10). In the paediatric population, 4% of brain tumours are associated with genetic syndromes, including neurofibromatosis, tuberous sclerosis, Sturge–Weber, Li–Fraumeni, and von Hippel-Lindau (8).

Pathophysiology

The pathophysiology of headache associated with intracranial neoplasm involves many mechanisms (11). The brain parenchyma itself is insensitive to pain, but brain vessels, meninges, bone, teeth, and sinuses are innervated and transmit sensory input through the trigemino-cervical complex (12). Neoplastic processes may elicit pain by different types of stimuli. Inflammation, thrombosis, perturbation of vascular flow, modification of ionic gradient and pH, and mechanical traction or pressure may all stimulate pain fibres (13,14). A mass expansion, peritumoral oedema, venous thrombosis, intra-tumoral haemorrhage, and hydrocephalus can lead to intracranial hypertension. Peritumoral oedema may be cytotoxic or vasogenic. Tumoral vessels with an abnormal permeability facilitate fluid leakage, increased by molecules such as glutamate, vascular endothelial growth factor (VEGF), and leukotrienes (15). The role of increased intracranial pressure in the generation of headache is uncertain. Sudden variations of intracranial pressure may be more significant than a stable elevated state (16).

Factors influencing the occurrence of headache

Headaches associated with brain tumours occur more frequently in children and young adults than in elderly patients, possibly because the impact of an expanding mass on intracranial pressure is less significant in an atrophic brain. In a study of 714 patients, headache was the presenting symptom for 44% of patients aged 18–24 years, and only 8% in the group aged > 75 years (17). In this age group cognitive symptoms are more frequent. Sex does not influence headache frequency, with only one study mentioning a trend for a higher prevalence in females (18). Patients with a prior history of headache are more likely to develop a headache as a symptom of a brain tumour. In

Table 47.1 ICHD-3 codes related to brain tumours.

Code	Diagnosis
5.5	Acute headache attributed to craniotomy
5.6	Persistent headache attributed to craniotomy
6.9	Headache attributed to pituitary apoplexy
7.1	Headache attributed to increased cerebrospinal fluid pressure Note: When the increase in intracranial pressure is attributed to a brain tumour, the code should be 7.4.
7.4 7.4.1 7.4.1.1 7.4.2 7.4.3	Headache attributed to intracranial neoplasia Headache attributed to intracranial neoplasm Headache attributed to colloid cyst of the third ventricle Headache attributed to carcinomatous meningitis Headache attributed to hypothalamic or pituitary hyper- or hyposecretion
7.5	Headache attributed to intrathecal injection
13.1.2.4	Painful trigeminal neuropathy attributed to other disorder
A5.7	Headache attributed to radiosurgery of the brain

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a study of 111 patients, 78% of patients with a history of headache had headache associated with their brain neoplasm versus only 33% in the group with no history of headache (19). Familial history of headache has been associated with headache caused by a brain mass (18–20).

Malignant tumours with a rapid growth rate, tumours located in the posterior fossa, and midline or basal tumours are more likely to cause headaches, and also seizures or focal neurological deficits (5,6,18,21). For glioblastomas, a bigger size is associated with a higher prevalence of headache. The size of a benign tumour itself is not associated with headache unless the cerebrospinal fluid flow is impaired (5,19). Intracranial hypertension is associated with a higher prevalence of headache (Table 47.2).

Is there a typical brain tumour headache?

Diagnostic criteria for headache attributed to a space-occupying lesion are listed in Box 47.1. In the second edition of the ICHD, if the headache did not improve after tumour treatment, the diagnosis could not be made. The third edition allows a diagnosis without post-treatment improvement, which has methodological implication for future studies. In ICHD-3, headache secondary to intracranial hypertension caused by a tumour must be coded as headache associated with intracranial neoplasm.

Headache caused by a brain tumour has no pathognomonic feature. The classical brain tumour headache, described as severe, worse in the morning, and associated with nausea and emesis is rarely encountered (Table 47.3), and is more likely to occur in the context of intracranial hypertension and with posterior fossa tumours. Nevertheless, such a presentation warrants immediate investigation. More commonly, brain tumour headache is described as dull, moderate, intermittent, and relieved by analgesics (Table 47.4). It may meet the ICHD-2 criteria for tension-type headache in 16–39% of cases and migraine in up to 13%, but atypical features such as progression and deterioration when lying down are frequently present and suggest a secondary aetiology (18,20).

The localization of the headache is a poor predictor of the site of the tumour (14,22). The pain is fronto-temporal in 30–68% and unilateral in 21–51% of cases. In this unilateral group, the pain is ipsilateral to the tumour in 41–100% of patients, with a better predictability in the absence of intracranial hypertension. Tumours adjacent to the skull or dura mater are more often associated with an ipsilateral headache (18). The localization of headache caused a by a posterior fossa tumour is debated. Infratentorial tumours tend to produce a posterior headache, present in 45% of patients versus only 13% of supratentorial tumours in one study (6,19,20). On the contrary, Pfund et al. (5) showed that posterior fossa tumours were associated with an occipital headache in only 23%, and with a frontal or periorbital headache in 77% of cases. The tentorial branches of V1 and V2 innervate the inferior part of the tentorium cerebelli, explaining this pain referral pattern (23–25). The higher prevalence of intracranial hypertension in this group may also lead to a more diffuse headache.

The headache caused by a brain tumour rarely remains the only symptom. An isolated headache occurs in 2–16% of patients (18,20,21,26,27). The longest duration of an isolated headache in one cohort was 77 days, which prompted the authors to suggest that a headache of more than 10 weeks' duration without other symptoms is very unlikely to be secondary to a brain tumour (21). However, other series report headache durations of more than 6 months in

Table 47.2 Prevalence of headache in brain tumour series.

Study	*n*	Headache % of cohort	% Headache supratentorial	% Headache infratentorial	Intracranial hypertension (% of cohort)	% of headache with ICH	% of headache with no ICH
Dowman and Smith (22)	100	37 initial 81 total	NA	NA	57	NA	NA
Rushton and Rooke (136)	221	60	58	64	27	92	47
Forsyth and Posner (19)	111	48	40	82	18	85	38
Snyder et al. (137)	101	56	NA	NA	28*	NA	
Suwanwela et al. (6)	171	71	60	84	40*	95	54
Pfund et al. (5)	279	59	55	76	NA	NA	NA
Schankin et al. (20)	85	60	57	71	None†	NA	NA
Valentinis et al. (18)	206	48	44	60	10	81	19

ICH, intracranial hypertension; NA, not available.

*Intracranial hypertension defined as presence of papilloedema. †Patients were treated with steroids.

Box 47.1 ICHD-3 classification criteria for the diagnosis of headache attributed to an intracranial neoplasia (7.4.1)

- **A** Any headache fulfilling criterion C.
- **B** A space-occupying intracranial neoplasm has been demonstrated.
- **C** Evidence of causation demonstrated by at least two of the following:
  - **1** Headache has developed in temporal relation to development of the neoplasm, or led to its discovery
  - **2** Either or both of the following:
    - (a) Headache has significantly worsened in parallel with worsening of the neoplasm
    - (b) Headache has significantly improved in temporal relation to successful treatment of the neoplasm
  - **3** Headache has at least one of the following four characteristics:
    - (a) Progressive
    - (b) Worse in the morning and/or when lying down
    - (c) Aggravated by Valsalva-like manoeuvres
    - (d) Accompanied by nausea and/or vomiting.
- **D** Not better accounted for by another ICHD-3 diagnosis.

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45% of cases and even of many years, but mostly with benign tumours (6,19). In children, headache can be isolated in 30% at 1 month from onset, but remains isolated in only 6% at 4 months (28). In a cohort of 3291 children with brain tumours, headache was the only symptom in < 1% and the neurological examination was normal in < 3% (29).

Investigation and management of headache related to a brain tumour

The decision to image or not

The decision to image a healthy patient with non-acute headache has been addressed in published guidelines (30–32). The importance of a careful history and examination cannot be overemphasized. The examination of fundi for papilloedema cannot be overlooked. Features more strongly associated with the discovery of a tumour include older age, awakening from sleep with headache, dizziness, rapidly increasing headache frequency, abnormal neurological examination, focal neurological symptoms, exacerbation with Valsalva manoeuvre, associated vomiting, and a progressively worsening headache of recent onset (Table 47.5) (33). A patient presenting to a general practitioner with headache has a 0.1% chance of having a brain neoplasm and even less for a malignant subtype (27). In children, the risk of finding a tumour may be higher. In a cohort of 397 children presenting with isolated headache, 4% had space-occupying lesions. The absence of migraine in the family and awakening from sleep are significant predictors (34). In the absence of any red flag, imaging is still performed in up to 40% of patients for reassurance purposes (35). Brain imaging may lead to the discovery of a serendipitous finding with subsequent need for follow-up and significant anxiety for the patient (36). A confident diagnosis of migraine lessens the probability of a secondary aetiology if no recent change is reported and the examination is normal (37). Explaining a primary headache diagnosis is probably better for the patient than performing unnecessary imaging. The risk of incidental findings even in the asymptomatic population is significant. In one study, 0.7% of 15,000 magnetic resonance images (MRIs) showed a neoplastic incidental finding, and 2% showed a non-neoplastic finding (38).

In patients with a history of cancer, imaging should be performed in all cases, even if the suspicion is low. Brain metastases occur in 20–40% of patients with cancer. The risk of finding a brain metastasis in a patient known for a neoplasia reporting a new or modified headache is 32.4% (39). Another study found a structural cause in 38 of 97 patients known to have cancer who presented an undiagnosed headache (40).

How to treat the headache associated with an intracranial mass?

Evidence regarding the treatment of headache secondary to an intracranial neoplasm is scarce. Most therapeutic trials focused on remission and the control of other neurological symptoms. Common analgesics bring relief in 42% of patients (20). A positive response is more likely in the absence of intracranial hypertension, and with benign tumours such as meningiomas (18,19). Steroids and antiepileptic drugs were used for 45% and 29% of 85 patients, respectively, in one study, but response rates were not reported (20). Corticosteroids decrease vasogenic oedema by downregulating VEGF and increasing angiopoietin 1, a blood–brain barrier stabilizer (41). Other VEGF-inhibiting agents are now used and allow a decrease in steroid use.

Table 47.3 Typical features of headaches associated with a brain tumour in different series.

Study	Severe	Worse night or morning	Nausea, vomiting	Exertional or Valsalva related	Classic triad
Rushton and Rooke (136)	37	25	46	23	NA
Forsyth and Posner (19)	NA	53	48	23	17
Suwanwela et al. (6)	37	71 at night 18 morning	36	18	NA
Pfund et al. (5)	55	72	60	NA	NA
Schankin et al. (20)*	Median 6/10	NA	17	9–11 2 (cough)	NA
Valentinis et al. (18)	Median 6/10	29 nocturnal 46 awaken during sleep	34 nausea 23 vomiting	19–30 1 (cough)	5

All data are percentage of the headache group studied. NA, not available.

*Patients were treated with steroids.

Table 47.4 Two presentations of the brain tumour headache.

Classical definition More likely if increased intracranial pressure	A severe headache, progressive, awakening the patient at night or worse upon waking up, triggered by exertion, Valsalva, and cough. Nausea and vomiting, sometimes projectile, are the rule. The headache lateralizes to the side of the lesion. The headache disappears after the treatment of the lesion
Common situation	A moderate, intermittent headache that may be dull or throbbing, sometimes associated with nausea or vomiting, relieved at least partially by analgesics. Provocation by exertion and Valsalva is not frequent, and very rarely seen with cough. Location of the headache is a poor predictor of tumour site. Headache may persist after treatment or even be caused by treatments.

Acetazolamide is expected to decrease intracranial pressure, and also enhances apoptosis and inflammation control when combined with temozolomide (42,43). The use of beta blockers was associated with a lower prevalence of headache in one study (20). Chemotherapy, radiosurgery, and surgery used for tumour control may lead to an improvement of the headache but may also cause a new secondary headache. Whole-brain radiotherapy improved the headache in 73–96% of patients with metastases (44). Tumour resection did lead to headache improvement for 98 of 116 patients in one study (18).

Colloid cysts and other paroxysmal headaches

Thunderclap headache (TCH) is a severe headache reaching a maximum intensity almost instantly (see also Chapter 34). Colloid cysts of the third ventricle and pituitary apoplexy associated with an underlying tumour are distinct neoplastic causes of TCH. Other aetiologies are more frequent in patients with intracranial neoplasia, including thrombotic events, cerebral venous thrombosis, and intra-tumoral bleeding (45). Intracranial hypotension may be the result of a postoperative cerebrospinal fluid leak or lumbar puncture.

Table 47.5 Chemotherapy and mechanisms for headache.

Chemotherapy	Secondary headache related to drug administration
All-trans retinoic acid-induced chemotherapy (oral)	Induction of pseudotumor cerebri (rare)
Bevacizumab (IV)	Headache reported as side effect, but also increased risk of thromboembolic event, haemorragic stroke, high blood pressure with associated headache
Carmustine (wafers in surgical cavity)	Headache is a rare side effect (0.39%) according to the FDA
Cytarabine (IT)	Acute arachnoiditis
L-asparaginase (IV or IT)	Increased risk of haemorrhagic and thrombotic strokes, including venous thrombosis
Methotrexate (IT)	Acute and subacute arachnoiditis
Procarbazine (oral)	Monoamine oxidase inhibitor activity associated with serotoninergic syndrome. May interact with triptans.
Steroids	Decrease symptoms but tapering may induce headache or trigger pseudotumor cerebri

IT, intrathecally; FDA, US Food and Drugs Administration; IV, intravenously.

Colloid cyst of the third ventricle

Colloid cysts of the third ventricle are benign neuroepithelial tumours representing 0.5–2% of all intracranial tumours (46). They affect men more often than women, and most cases reported were diagnosed between 20 and 50 years old, although they can be diagnosed at any age (47). These cysts are less common in children, but, if present, are more aggressive than in adult patients.

Headache is the most frequent symptom of ventricular colloid cysts, reported in 68–100% of patients (48). It is the presenting symptom in 75% of cases. The classic presentation is a paroxysmal severe headache accompanied by nausea, vomiting, visual disturbances, and even loss of consciousness. The headache is more frequently anterior and bilateral, but posterior or unilateral cases have been described. The 'thunderclap' pattern is present when the cyst, acting like a valve, suddenly blocks the foramen of Monro, causing an acute obstructive hydrocephalus. The pain will generally increase or be triggered by coughing, sneezing, or any Valsalva manoeuvre. Positional changes can provoke or relieve the symptoms. However, patients with other brain tumours may also experience Valsalva- or cough-related headaches, so this feature is not entirely specific. Duration in colloid cysts is typically < 30 minutes, but may be more than a day and throbbing, sometimes leading to an erroneous diagnosis of migraine, if recurrent. Colloid cysts may produce a phenotype resembling idiopathic intracranial hypertension, with chronic headache and papilloedema. Papilloedema is present in 20–72% of patients, but in one study 72% had a completely normal examination (47,49). In an analysis of 39 cysts, half were not clinically suspected at presentation and 20% were found incidentally (49). A pineal cyst may produce a similar phenotype, sometimes associated with convergence limitation and Parinaud syndrome. Dysautonomic symptoms such as bradycardia, tachycardia, sweating, and abdominal pain may occur and, as a result, evoke the possibility of a phaeochromocytoma. Less frequent manifestations are sudden paralysis of the lower limbs, incontinence, memory deterioration, diplopia, dizziness, blurred vision, and ataxia.

Colloid cyst may be isodense and missed in 30% of computed tomography (CT) scans. MRI is more sensitive, but in rare cases, if the protein content of the cyst is low, the lesion will be isointense rather than hyperintense in T1-weighted imaging and can be missed. Also, if a colloid cyst is very small in diameter (< 5 mm) a conventional MRI study with 5-mm-thick slices can miss the lesion. Other lesions of the anterior third ventricle include meningiomas, choroid plexus papillomas, hamartomas, craniopharyngiomas, gliomas, and vascular and granulomatous lesions.

Sudden death is reported with colloid cysts, sometimes only a few days after presentation. Sudden deaths triggered by air travel have been reported (50). Acute intracranial hypertension with brain herniation and compression of the cardiovascular regulatory centres in the hypothalamus are the hypothesized mechanisms (51). Management is based on surgical approaches including ventriculo-atrial or ventriculo-peritoneal shunting in the acute setting, followed by endoscopic aspiration and microsurgical resection. The endoscopic procedure is less invasive but has a higher risk of recurrence. Microsurgical resection is still the standard of care. As no clinical

factor is reliable to predict the evolution of the cyst, a prompt evaluation and treatment is recommended in all cases (52,53).

Pituitary apoplexy

Pituitary apoplexy is a complication of 2–7% of pituitary tumours (54,55). In up to 80% of cases it is the presenting symptom of the tumour (56,57). The classical clinical picture is an acute or TCH, accompanied by visual deficits, oculomotor palsy, meningismus, vomiting, and an altered state of consciousness (see also Chapter 34). Silent apoplexy may be found in 25% of surgically removed adenomas. Sex, age, size of the tumour, and histological subtype, have not been found to predispose to apoplexy. Many precipitants have been described, including anticoagulants, high oestrogen states, irradiation, surgery, endocrinological provocative testing, hypotension, head trauma, postpartum state, transient increase in intracranial pressure, diabetes, and hypertension (56). Imaging with CT scan is not sufficient, and MRI is mandatory. Treatment may be supportive, including steroid replacement, but surgery is indicated if a neuro-ophthalmological compromise is present (54).

Leptomeningeal carcinomatosis

Leptomeningeal carcinomatosis is present in 1–5% of patients with solid tumours, the most common being lung and breast cancer and melanoma, but primary brain tumours can also disseminate. Haematological malignancies carry a higher 5–15% risk of carcinomatosis. Most often, it occurs in the setting of disseminated cancer, but 20% of cases present after a disease-free interval and in 5–10% it is the initial manifestation of cancer (58). The subarachnoid space can act as a 'sanctuary site' for tumour cells, even if the systemic disease is controlled because a number of chemotherapeutic agents are not able to cross the blood–brain barrier.

The clinical manifestations related to leptomeningeal carcinomatosis can be multifocal and originate from the meninges in the vicinity of the hemispheres, the cranial nerves, or the spinal cord and roots (59,60). Headache is the most frequent symptom at presentation, occurring in 39% of cases. Intracranial hypertension may be caused by CSF flow disruption or associated venous sinus thrombosis (61). Other symptoms include confusion (12%), dizziness (4%), gait impairment (4%), aphasia (4%), and fatigue (2%). Deficits of the cranial nerves are present in 30–50% of patients (58). Seizures may occur. If this condition is suspected, a gadolinium-enhanced MRI of the entire neuraxis should be performed. The MRI should be done before the lumbar puncture to avoid a bias in the enhancement pattern. Cytology has a sensitivity of 71% after one sample, 86% after two samples, 90% after three samples, and 93% after more than three samples. Flow cytometry added to the cytology is significantly more sensitive if the primary is a haematological malignancy (62). The average time of survival is 2–3 months after diagnosis. Fifteen per cent of patients survive 1 year with current treatments (63).

Pituitary tumours and trigeminal autonomic cephalalgias

The prevalence of pituitary adenomas is estimated between 19 and 94 cases per 100,000 in the population (64). Pituitary incidentalomas are found in 3–10% of asymptomatic individuals with imaging and 3–27% of autopsies (65–68). Pituitary adenomas are most often benign and are categorized according to their size (a microadenoma if < 10 mm, a macroadenoma if > 10 mm) and hormone secretion characteristics. Prolactinoma is the most common subtype, representing 25–41% of all adenomas. A mild hyperprolactinaemia may also be found in non-secreting tumours if the pituitary stalk is compressed, impairing the inhibitory action of dopamine.

TACs include cluster headache, paroxysmal hemicranias, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), short-lasting unilateral neuralgiform headache attacks with cranial autonomic features (SUNA), and hemicrania continua (HC), and are characterized by attacks of unilateral pain accompanied by dysautonomic symtoms (see also Chapters 17–22) (69). The frequency and duration of attacks help to distinguish the different syndromes. Response to indomethacin is a diagnostic criterion for paroxysmal hemicrania and HC.

Epidemiology

Although the majority of headaches associated with pituitary tumours are migrainous or tension-type, TACs are over-represented when compared to their very low prevalence in the general population. Pituitary adenomas are associated with headache in 33–71% of cases, which is similar to the prevalence observed with other brain tumours (70–76). Headache may be the main presenting symptom in 11% of men and 15% of women, but visual and endocrinological symptoms are also frequent (77). In the majority of series, headaches associated with pituitary tumours have not been described or classified according to the international classification of headache disorders (70,71,75,78). Two studies used the ICHD-2 classification. Levy (79) reported 84 patients with pituitary tumours associated with headaches. In this study, 76% of patients had migraine, 27% primary stabbing headache, 5% SUNCT, 4% cluster headache, 1% HC, and the headache could not be classified in 7%. Schankin et al. (80) reported 58 patients of whom 41% had headache attributed to the tumour. The phenotype was migrainous (29%), tension-type (46%), mixed migrainous and tension-type (13%), cluster (4%), and unclassified (8%) (80).

The prevalence of pituitary tumours in TACs series is difficult to estimate, as symptomatic cases are likely to be excluded and published as individual cases. An analysis of 74 cases of chronic paroxysmal hemicranias included one case of pituitary tumour, not exceeding the expected prevalence (81). In a series of 52 SUNCT and SUNA cases, three patients (8%) had pituitary lesions (82). In a smaller series of 24 cases, no tumour was found, but Chitsantikul and Becker (83,84) reported six consecutive SUNCT and SUNA cases, five with an underlying tumour. In a review of 40 secondary TACs, 17 cases were associated with a pituitary tumour (85). Up to 2016, a total of 37 cases of TACs associated with a pituitary tumours have been published, including 21 SUNCT and SUNA, three HC, four paroxysmal hemicrania, and nine cluster headaches (Table 47.6). Twenty-six tumours were secreting prolactin or had mildly elevated prolactin levels, six secreted growth hormone (GH), one was mixed, and only three were non-secreting. The age at onset of headache varied between 18 and 56 years, with a mean of 38 years. All cases of cluster headache cases were male. For SUNCT, there were 10 males and 11 females. The duration of the TAC prior diagnosis is highly variable, and may be of many years. Attacks may be typical, although unusual

Table 47.6 Facial pain syndromes caused by intracranial neoplasia.

Syndrome, localization	Symptoms
Orbit	Supraorbital pain, proptosis, oculomotor palsy
Parasellar	Unilateral frontal headache, bitemporal hemianopsia, diplopia, no proptosis
Middle fossa	Pain, numbness, or paraesthesia in the V2 and/or V3 territory, oculomotor palsy
Jugular foramen	Hoarseness, vocal cord paralysis, glossopharyngeal neuralgia, atrophy of the tongue, palate, sternocleidomastoid and trapezius muscle
Occipital condyle	Severe and localized unilateral occipital pain, unilateral hypoglossal nerve palsy

triggers have been described, such as eating, cold wind, and postural changes. Other atypical traits may be refractoriness to usual treatments, persistent dysautonomic symptoms, and other neurological deficits. Symptoms like amenorrhoea, galactorrhoea, gynecomastia, impotence, and typical acromegalic features should be searched for, but their absence does not exclude an underlying structural lesion.

Pathophysiology

Both mechanical and functional factors may explain the link between pituitary tumours and TACs. The parasellar area and the cavernous sinus contain many structures richly innervated by sensory fibres (86). In almost all cases of TACs associated with pituitary tumours, the pain was ipsilateral to the lesion, which supports a mechanical effect. Numerous cases and series of TACs secondary to tumoral, infectious, and vascular sellar or parasellar lesions with no major endocrinological repercussions have been reported (85). It is therefore surprising that tumours of a larger size or invading the cavernous sinus do not produce more headaches (70,80,87,88). Imaging with MRI may be normal early in the course of the headache (83,89). Arafah et al. (78) suggested that size is not as important as local pressure effects. They studied the mean intrasellar pressure (MISP) in 49 cases of pituitary tumors undergoing surgery and found a higher MISP in patients with headache (not necessarily TACs). Size was not correlated with headache or a higher MISP. Mechanical factors in isolation do not seem sufficient to explain the pituitary–TAC relationship.

A disruption of the hypothalamic–pituitary axis probably contributes to the pathophysiology of secondary TACs. The hypothalamic–pituitary function is often abnormal in primary cluster headache and hyperactivation of the posterior hypothalamus has been shown during cluster headache attacks (90,91). Secreting adenomas are more likely to produce headaches and TACs, in particular, but either GH or prolactin-secreting tumours may be associated with TACs, suggesting that those hormones are not the exclusive culprits of the attacks. Other important variations of hormonal levels, for example physiological hyperprolactinaemia during breastfeeding, are not reported to induce TACs. Dopamine agonists are widely used for other indications, with no reported association with TACs in the absence of a tumour. Treatment with dopamine agonists has been shown to treat or trigger TACs. The mechanism linking an endocrinological perturbation to the activation of the trigeminovascular system has not been elucidated. Vasoactive intestinal peptide, calcitonin gene-related peptide, and neuropeptide Y levels did not correlate with headache in small studies not including TACs (92–94). Endocrinological imbalance may alter the functional activity or connectivity of hypothalamic structures and subsequently lead to an activation of the trigeminal nucleus. In four cases of cluster headache secondary to a pituitary tumour, da Freitas found an ictal hyperactivity in the hypothalamic area on single-photon emission emission CT, not present in other headache phenotypes (95).

Management

Investigation for an underlying pituitary tumour should be done in any patient with chronic cluster headache, SUNCT, SUNA, paroxysmal hemicranias, and HC, even if symptoms have been present for years. MRI with sellar views and gadolinium should be performed at least once, and repeated if the headache persists after 1 or 2 years. Blood tests should include prolactin, GH, insulin-like growth factor 1 (IGF-1), thyroid-stimulating hormone, adrenocorticotropic hormone (ACTH), and cortisol. IGF-1 has a longer half-life than GH and is more sensitive for screening (96). Some authors recommend the measurement of follicle-stimulating hormone, luteinizing hormone, oestrogen, and testosterone as well, although the diagnostic benefit is less clear. In the case of episodic cluster headache, well-controlled by usual treatments and with no atypical features, investigation is not mandatory, but in view of availability of imaging, it can be considered.

Dopamine agonists are the first line of treatment for prolactinomas with no visual impairment, regardless of headache. Interestingly, dopamine has a chemical resemblance to ergot alkaloids (97). Dopamine agonists (including bromocriptine, cabergoline, lisuride, and quinagolide) have been tried in 13 patients with SUNCT (**Table 47.7**), leading to an improvement in three, no effect in two, and deterioration in seven. In three cases dopamine agonists triggered SUNCT in previously asymptomatic patients (98,99). The effect of dopamine agonists is more positive for cluster headache. In five cases of cluster headache associated with prolactinomas, three were completely controlled by cabergoline. Octreotide, a somatostatin analogue and GH inhibitor, may be used to control headaches associated with GH adenomas, but may also treat primary TACs (100,101). Octreotide inhibits the synthesis of substance P (102). A tolerance syndrome may occur and force the withdrawal of the drug.

In the four cases of paroxysmal hemicrania, three improved with indomethacin, but the symptoms then completely resolved after surgery, allowing cessation of the drug. Surgery is indicated for all GH-secreting adenomas to avoid the complications of acromegaly but is not necessarily performed for other types of adenomas in the absence of visual deficit. Of the 19 cases of TAC where the tumour was surgically removed, 17 lead to a sustained cessation of symptoms, suggesting that surgery can be considered to treat the headaches, regardless of the size of the lesion. In one case, surgery followed by radiotherapy did trigger SUNCT (103). If the pituitary tumour is associated with another type of headache than a TAC, surgical series report improvement in 50–85% of cases, but deterioration may be seen in 15% (70,76,79,80,88,104). Interventional approaches can be considered in refractory cases. da Freitas (95) reported 11 cases of unilateral headaches (TAC and migraine-like) not improved by surgery. Five were controlled medically. The six others had a percutaneous trigeminal ganglion blockade, with a durable

Table 47.7 Characteristics of the headache associated with an intracranial mass.

Series	Unilateral	Ipsilateral	Tension-type headache	Migraine	Intermittent	Throbbing
Forsyth and Posner (19)	25	100	77	9	62	NR
Suwanwela et al. (6)	21	80	NR	NR	78	26
Pfund et al. (5)	NR	41	16	7	88	63
Schankin et al. (20)	51	61	39	0	> 60	15
Valentinis et al. (18)	29	82	23	13	NR	NR

All data are percentage of the headache group studied except for the data in the ipsilateral column, which shows percentage of the unilateral headache group. NM, not reported.

benefit in one migraine case, and a transient improvement in two cluster cases. Those two patients underwent a balloon trigeminal rhizotomy with a sustained benefit. To date, there has been no report of neurostimulation for a TAC associated with a pituitary tumour.

Headaches related to the treatment of tumours

Chemotherapy

The specific effects of chemotherapy on head pain are summarized in Table 47.8. Bevacizumab, an anti-VEGF medication, and L-asparaginase are associated with an increased risk of vascular events, including venous thrombosis and intracerebral haemorrhage (105). Temozolomide may cause a severe headache in 5% of patients (106). Procarbazine has a monoamine oxidase-inhibiting activity and carries a theoretical risk of serotoninergic syndrome (107). Carmustine wafers are used in the surgical cavity and do not seem to be associated with headache (108). Lumbar puncture can be performed to make a diagnostic or administer chemotherapy. Post-lumbar puncture headache, characterized by orthostatic symptoms, is a risk with each procedure and may be avoided by using small-gauge atraumatic needles (109). Intrathecal chemotherapy with methotrexate or cytarabine can induce aseptic meningitis characterized by an acute onset of fever, headache, and stiff neck (110). Opportunistic infections have to be ruled out. Usually, the patient recovers within a few days (111). Ondansetron, frequently used as an antiemetic agent, has been reported to induce headaches mimicking migraine, even in non-migrainous patients (112,113). Secondary pseudotumor cerebri has been associated to Addison disease or primary adrenal insufficiency (114,115). It can also be triggered by rapid lowering of steroid blood levels, such as removal of an ACTH-producing tumour or decreasing doses of oral corticosteroids (116). All-trans retinoic acid-induced chemotherapy is a derivative of vitamin A used for the treatment of promyelocytic leukaemia reported to induce pseudotumor cerebri (117).

Radiotherapy

Radiotherapy can induce an acute headache in 11–20% of patients, which is usually self-limited or responsive to steroids (118). Radiotherapy is also associated with various vascular complications, including moyamoya disease, arterial dissection, reversible cerebral vasoconstriction syndrome, vasculitis, and chronic mild ischaemia. The stroke-like migraine attacks after radiotherapy syndrome presents with headache, neurological deficits, and seizures, occurs 2–10 years after the radiation, and mimics tumour recurrence. It can remit spontaneously (119).

Surgery

Headache is the most frequent complication following craniotomy. Various pathophysiological mechanisms are suggested, including adherence of cervical muscles and subcutaneous tissue to the highly innervated dura, dural tension during closure, and surgical stress on major muscles, such as the temporalis, splenium capitis, and cervicis in the case of suboccipital or subtemporal craniotomies (120). Acute post-craniotomy headache is present in 70% of patients on the first day, 50% on the second day, and may persist for weeks (121). Women, younger patients, and those who require opioids before surgery are more at risk of postoperative pain (122). The pain is frequently centred near the surgical wound, but can be more diffuse, with or without migrainous features. Acute post-craniotomy headache is probably underestimated and undertreated, despite a significant impact on quality of life. Chronic post-craniotomy headache

Table 47.8 Best estimates of risk of tumour with headache presentations in primary care and associated features.

Clinical feature	Likelihood ratio (95% CIs)	Risk of tumour in headache presentations in primary care (%)
Headache causing waking from sleep	98 (10–960)	9
Dizziness or lack of coordination	49 (3–710)	4
Rapidly increasing headache frequency	12 (3–48)	1
Abnormal neurological examination	5.3 (2.4–12)	0.5
Headache with focal neurological symptoms	3.1 (0.37–25)	0.3
Aggravated by exertion or Valsalva-like manoeuvre	2.3 (1.4–3.8)	0.2
Associated vomiting	1.8 (1.2–2.6)	0.2
Worsening headache	1.76 (0.23–10)	0.1

Derived from primary care pretest probability (0.09%) and likelihood ratios derived mainly from secondary care. CI, confidence interval.

Source data from *British Journal of General Practice*, 58, Kernick DP, Ahmed F, Bahra A, et al. Imaging patients with suspected brain tumour: guidance for primary care, pp. 880–885, 2008.

(CPCH) is by definition persisting for more than 3 months. It may be localized or diffuse, with or without a neuropathic component. Incidence of CPCH is variable but is higher in females and associated with depression and anxiety. Posterior fossa surgeries carry a higher risk than supratentorial interventions. Acoustic neuromas rarely cause headache, but their resection is followed by CPCH in up to 64% of cases, the risk being higher with the suboccipital approach (123). This surgery has been associated with a particular form of headache, typically paroxysmal, lasting a few minutes to 2 hours and triggered by coughing, bending, and straining (124). Pre-operative steroid administration seems to attenuate post-craniotomy pain intensity (125). Data on adequate management of post-craniotomy headache is lacking, but options include non-steroidal anti-inflammatory drugs, acetaminophen, and narcotics (126). Gabapentin lowers the need for analgesics in the acute setting and decreases the occurrence of chronic postoperative pain, but there is yet no trial on CPCH prevention. Local scalp blocks have been shown to decrease CPHC from 56% to 8% in one study (127). Headache after acoustic neuroma surgery usually responds to anti-inflammatories, but refractory cases may justify a surgical decompression of the greater occipital nerve (128).

Other headache syndromes related to intracranial neoplasia

Intracranial tumours may produce any neurological deficit based on local invasion and destruction adjacent structures. Specific syndromes based on anatomy are presented in Table 47.9. In an early study, Bullitt et al. (129) described 2000 cases of facial pain,

Table 47.9 Trigeminal autonomic cephalalgias (TACs) and pituitary tumours.

Reference	TAC	Sex/age (y)	Years before diagnosis	Size/hormone	Treatment	Efficacy
Cluster headache (CH)						
Tfelt-Hansen et al. (138)	CH	M/52	31	Macro/PRL	Surgery	Resolves
Milos et al. (139)	CH	M/37	9	Micro/GH	Surgery	Resolves
Porta-Etessam et al. (140)	EH	M/30	2	Macro/PRL	Cabergoline	Resolves symptoms and tumour
Leone et al. (141)	CH	M/49	3	Macro/PRL	Cabergoline Surgery	No effect Resolves
Negoro et al. (89)	CH	M/17	3	NR/PRL	Cabergoline	Resolves symptoms and tumour
Soto-Cabrera et al. (142)	CH	M/34	6	Macro/PRL	Cabergoline	Resolves symptoms and tumour
Benitez Rosario et al. (143)	CH	M/41	1	Macro/PRL	Cabergoline Octreotide No surgery	No details Improved
Levy et al. (144)	CH	M/25	< 1	Macro/ PRL	Cabergoline	Resolves symptoms and tumour
Edvardsson (145)	CH	M/49	1 month	Macro/NA	Surgery	Resolves
Paroxysmal hemicrania (PH)						
Greve and Mai (146)	PH	M/58	2	Macro/PRL	Bromocriptin Indomethacin not tried	Improves symptoms and tumour
Gatzonis et al. (147)	PH	M/20	1.5	Macro/TSH, ACTH, PRL	Indomethacin Surgery	Improves Resolves
Boes and Dodick (81)	PH	M/41	7	Macro/PRL	Indomethacin Surgery	Improves Resolves
Sarov et al. (148)	PH	F/27	1	Macro/PRL	Indomethacin Cabergoline	Improves Resolves
Hemicrania continua (HC)						
Marzocchi et al. (149)	HC	M/66	> 20	Micro/GH	Surgery	Improves
Levy et al. (150)	HC	F/40	1	Micro/PRL	DA agonists Indomethacin	Deteriorate Improves
Levy et al. (151)	HC	F/29	1	NR/GH	Surgery Octreotide Lanreotide	No effect Improves No effect

(*continued*)

Table 47.9 *Continued*

Reference	TAC	Sex/age (y)	Years before diagnosis	Size/hormone	Treatment	Efficacy
SUNCT/SUNA						
Ferrari et al. (152)	SUNCT	M/51	10	Size? Non-secreting GH (biopsy)	Bromocriptine Surgery	Triggers Resolves
Massiou et al. (153): Case 1	SUNCT	F/40	3	Macro/PRL	Bromocriptine Cabergoline Lisuride Radiotherapy	Triggers Triggers Triggers Improves
Massiou et al. (153): Case 2	SUNCT	F/24	4	Micro/PRL	Bromocriptine Lisuride Surgery	Triggers Triggers Not mentioned
Levy (150)	SUNCT	F/36	1	Micro/PRL	Bromocriptine Cabergoline Surgery	Deteriorates Deteriorates Improves
Matharu et al. (154)	SUNCT	M/37	11	Macro/PRL	Bromocriptine Cabergoline	Resolves
Larner (99)	SUNCT	M/43	NR	Micro/ PRL	DA agonist (stopped)	Triggers
Leroux et al. (155)	SUNCT	M/28	10	Micro/PRL	DA agonist Surgery	Deteriorates Resolves
Rocha-Filho et al. (156)	SUNCT	M/38	12	Macro/non-secreting	Surgery	Resolves
Rozen (157)	SUNCT	M/37	4	Micro/GH	Surgery	Resolves
Jimenez Caballero (98)	SUNCT	F/22	NR	Size? PRL	Cabergoline (stopped)	Triggers (size decrease)
Adamo et al. (158)	SUNCT	M/38	5	Micro/GH	Surgery	Resolves
Zidverc-Trajkovic et al. (159)	SUNCT	F/27	6	Micro/PRL	Bromocriptine Lamotrigine	No effect Efficient
de Lourdes Figuerola et al. (160)	SUNCT	M/51	4	Macro/PRL	Cabergoline	Resolves
Chitsantikul and Becker (83): Case 1	SUNCT	M/45	3	Macro/mixed	DA agonists Surgery	Not tolerated Low benefit Improves
Chitsantikul and Becker (83):Case 2	SUNCT	F/25	6	Micro/PRL	Surgery	No improvement
Chitsantikul and Becker (83): Case 3	SUNCT	F/56	< 1	Micro/NA	Surgery	No improvement
Chitsantikul and Becker (83): Case 4	SUNCT	F/30	12	Micro/PRL	Bromocriptine Surgery	Not tolerated Improvement then recurrent
Chitsantikul and Becker (83): Case 5	SUNCT	F/51	4	Macro/PRL	Cabergoline Surgery	Small benefit Improvement
Musuka et al. (161)	SUNCT	M/43	10	Micro/PRL	DA agonist	Improves
Pulido-Fontes et al. (162)	SUNCT	M/24	NR	Macro/PRL	Cabergoline Quinagolide	Triggers Improves
Berk and Silberstein (103)	SUNCT	F/35	NR	Macro/NA	Radiosurgery	Triggers

M, male; PRL, prolactin; GH, growth hormone; NR, not reported; NA, not available; TSH, thyroid-stimulating hormone; ACTH, adrenocorticotropic hormone; F, female; DA, dopamine; SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; SUNA, short-lasting unilateral neuralgiform headache attacks with cranial autonomic features.

approximately 1% were caused by an intracranial tumour. Unilateral severe facial pain radiating to the ear may be caused by ipsilateral non-metastatic lung cancer (130). The pain may be caused by infiltration of the vagus nerve. Weight loss, clubbing of the fingers, and an elevated sedimentation rate in a current or ex-smoker are clues that should prompt the search for a pulmonary lesion.

Trigeminal neuralgia (TN) can be secondary to a brain tumour along the pathway of the nerve or in the brainstem (see also Chapter 27). Between 5% and 16% of cases of TN may have an underlying tumour. A sensory loss or any other cranial nerve deficit is an important clinical clue (131,132). Secondary temporomandibular disorder and persistent idiopathic facial pain

may be encountered, but these are more frequently seen by dentists. Also, malignant peripheral nerve sheaths tumours are rare aggressive malignancies arising from Schwann cells that can lead to TN (133).

Migraine with aura is rarely associated with an underlying tumour. In a review of 40 cases of aura secondary to a brain lesion, seven cases were related to a neoplasia, including three meningiomas, one metastasis, one oligodendroglioma, one subependymoma, and one astrocytoma (134). These lesions are often occipital, but parietal and temporal localizations are also described.

A single case of nummular headache caused by a meningioma has been reported (135). This 'coin-shaped' headache is mostly primary, but secondary aetiologies have to be ruled out by appropriate imaging (see also Chapter 33).

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48

Headache and Chiari malformation

Dagny Holle and Julio Pascual

Introduction

In the late nineteenth century, the Austrian pathologist Hans Chiari (1851–1916) described a group of syndromes characterized by pathological conditions of posterior fossa hindbrain development and which are now summarized as Chiari malformations (1).

Four types can be distinguished (Table 48.1). Most of the cases are congenital; few are acquired after birth. Reasons for development are multifactorial and often enigmatic (Table 48.2). Owing to the variable underlying pathophysiology, the clinical presentation of Chiari malformation is highly diverse.

Chiari malformation type I is the most frequent subtype, with headache as the most frequent clinical presentation. However, Chiari malformations may be found incidentally in patients without symptoms related to the malformation. Usually, the presence of a Chiari malformation type I malformation is first noticed in adolescence or adulthood. When symptomatic, Chiari malformation type I has to be differentiated from compression of the brainstem or spinal cord, and from hydrocephalus, endolymphatic hydrops, and pseudotumor-like episodes (2). Chiari malformation type II is usually accompanied by a myelomeningocele. Chiari malformation type III is the most serious subtype of CM and causes severe neurological symptoms. Chiari malformation type IV is a rare subtype, characterized by cerebellar hypoplasia. Chiari malformation types II–IV are predominantly diagnosed in children, sometimes even before birth. Severe neurological deficits characterize the latter subtypes. This chapter mainly focuses on Chiari malformation type I.

Epidemiology

The prevalence of Chiari malformation type I is unknown and population-based data are not available. The increasing availability of magnetic resonance imaging (MRI) has led to an increase in the finding of (often asymptomatic) Chiari malformation type I. Chiari malformation type I is present in approximately 1–2 newborn infants per 1000 births (3).

Chiari malformation type I is often associated with other conditions such as hydrocephalus, syringomyelia, spina bifida, spinal curvature, tethered spinal cord syndrome, and connective tissue disorders such as Ehlers–Danlos syndrome and Marfan syndrome (4).

Clinical presentation

Most symptoms in Chiari malformation type I start around the age of 30 years and are referred to as 'adult cases', but symptoms can also be experienced in patients at a younger age. The clinical presentation of Chiari malformation type I can be complex and heterogeneous (5). Symptoms include headache, nystagmus, ataxia, dysphagia, and visual disturbances (Table 48.3), with headache as the most often reported clinical feature. A retrospective review of 50 patients with Chiari malformation type I showed that 50% had a headache disorder (6). The type of headache varied from patient to patient. Twenty-eight per cent of the patients reported a typical suboccipital or occipital headache, aggravated by Valsalva manoeuvre, effort, cough, or postural changes. The quality and duration of pain was variable. Migraine or tension-type headache was experienced by 22% of this cohort—similar to the prevalence in the general population. In a prospective study, 81% of 364 patients with Chiari malformation type I suffered from headache (2). Pain was mainly suboccipital and radiated to the vertex, behind the eyes and to the neck or shoulder. Suboccipital localization was also confirmed in other studies (7). The pain was characterized as heavy and crushing or pressure-like. All patients reported an accentuation of headache intensity due to physical exertion or Valsalva manoeuvre (2). Even a few cases of 'laugh headache' in Chiari malformation type I are reported in the literature in which laughing induced a severe occipital pain that disappeared after cessation of laughter. A study of 265 patients with Chiari malformation type I with or without syringomyelia showed that 98% of patients complained of headache (Table 48.4) (8).

Interestingly, in migraine patients with Chiari malformation type I, the occurrence of chronic migraine may be increased (9). In 73 patients with Chiari malformation type I, 11 (15.1%) suffered from migraine. Of these patients eight (11.0%) had a pattern of chronic migraine, which is a much higher percentage than in a control group of migraineurs without Chiari malformation type I. Clinical features of migraine, however, were different between the two patient groups. In patients with Chiari malformation type I migraine started earlier, headaches were more frequent, and baseline pain intensity and aggravation of headache with physical activity was increased. Besides, patients more often reported migraine-associated nausea and vomiting. The relationship

Table 48.1 Classification of Chiari malformations.

Malformation type	Description
Type I	Congenital malformation Elongation of the tonsils and the medial parts of the inferior lobes of the cerebellum into cone-shaped projections, which accompany the medulla oblongata into the spinal canal
Type II	Displacement of parts of the inferior vermis, pons, and medulla oblongata together with elongation of the fourth ventricle (most cases are associated with spina bifida)
Type III	The entire cerebellum herniates into the cervical canal
Type IV	Cerebellar hypoplasia

between chronic migraine and Chiari malformation type I, however, has to be proven (10). In most cases it may be coincidental. In our series, only one of 100 consecutive patients with chronic migraine showed tonsillar descent (**Figure 48.1**).

In another study, we analysed 72 cases of cough, exertional, and sexual headache (11), and found that all 17 patients with symptomatic cough headache had a Chiari malformation type I. In contrast, symptomatic exertional headaches and sexual headaches were mainly secondary to subarachnoid haemorrhage.

Pathophysiology

It has been suggested that the typical symptom of cough headache in Chiari malformation type I is caused by peaks in intrathecal pressure, leading to obstruction of cerebrospinal fluid (CSF) flow. One study investigated peak intrathecal pressure during cough and without coughing in patients with cough headache associated with Chiari malformation type I compared with healthy controls (12). In patients with Chiari malformation type I coughing was, indeed, associated with sudden increase of intrathecal pressure. After surgery (i.e. suboccipital craniectomy, C-1 laminectomy, and duraplasty), pressure increase during coughing was significantly lower and the headache had resolved partially or completely. In another study the degree of tonsillar herniation correlated significantly with the presence of headache (6), but this was not confirmed (13).

Headache in Chiari malformation type I might also be caused by intracranial hypertension due to a hydrocephalus, which is often observed as an associated pathology (14). Another hypothesis suggests that low-pressure headache can lead to a pseudo-Chiari malformation by inducing a tonsillar herniation similar to the one seen in Chiari malformation type I (14).

Differential diagnosis

Clinical experience has shown that Chiari malformation type I does not cause a headache consistent with the clinical presentation of an idiopathic primary headache disorder. Only a few case reports have described both conditions in the same patient (13,15). In patients with symptomatic Chiari malformation, the prevalence of other

Table 48.2 Congenital and acquired causes of Chiari malformations.

Congenital causes	Acquired causes
• Genetic mutations • Lack of maternal vitamins • Lack of maternal nutrients	• Excessive draining of spinal fluid • Injuries • Infections • Chronic subdural haematoma

idiopathic primary headache disorders was not increased (6). Most important in patients with cough headache is to determine whether it is primary or secondary (see also Chapter 24) (16). Primary cough headache should be suspected in patients older than 50 years of age, with pain that does not predominate in the occipital area, lasting seconds, without other symptoms/signs and relieved by indomethacin. Secondary cough headache due to a Chiari type I malformation should be suspected in young people, when pain is occipital, lasts longer than 1 minute, has other symptoms/signs, and has no response to indomethacin. It is thus recommended that every patient with cough headache is analysed with a brain and cervical spine MRI.

Low intracranial pressure headache might mimic Chiari malformation type 1 (see also Chapter 38). All patients should be questioned regarding previous lumbar punctures or epidural anaesthesia procedures. Additionally, evaluating patients for trauma or spontaneous CSF leaks and intracranial hypotension should be done to avoid the erroneous diagnosis of Chiari malformation type 1 in patients with tonsillar descent from low CSF pressure. The presence of orthostatic headache and a gadolinium-enhanced MRI of the brain and MRI of the spine should be performed when there is an index of suspicion for a CSF leak (17).

Other causes of headache such as infections, trauma, hypertension, sinus, ocular disorders, or somatisation should be ruled out (18).

Table 48.3 Most common symptoms in Chiari malformation type I .

Symptoms	%
Headache	98
Dizziness	84
Difficulty sleeping	72
Weakness in arms/hands	69
Neck pain	67
Numbness/tingling in arm, hands	62
Fatigue	59
Nausea	58
Shortness of breath	57
Blurred vision	57
Tinnitus	56
Difficulty swallowing	54
Leg weakness	52

Mueller DM, Oro' JJ. Prospective analysis of presenting symptoms among 265 patients with radiographic evidence of Chiari malformation type I with or without syringomyelia. *J. Am. Acad. Nurse Pract.* 2004;16:134–138.

Table 48.4 Headache types observed in patients with Chiari malformation.

Headache type	Association with Chiari malformation	Clinical presentation
Cough headache	Typically seen in patients with Chiari malformation	Sudden onset during coughing, lasting from 1 s to 30 min
Laughing headache	Observed in some patients with Chiari malformation	
Exertion-induced headache	Typically seen in patients with Chiari malformation	Similar to coughing headache
Chronic migraine	Increased prevalence in Chiari malformation compared with the general population	Migraine without aura on ≥ 15 days/month for > 3 months
Episodic migraine	Prevalence in Chiari malformation is equivalent to prevalence in general population	Headache lasting 4–72 h. Often unilateral location, pulsating quality, moderate or severe pain intensity, aggravating by routine physical activity, accompanied by nausea/vomiting, phono-/photophobia
Tension-type headache	Prevalence in Chiari malformation is equivalent to prevalence in general population	Headache lasting from 30 min to 7 days, Often bilateral location, pressing/tightening quality, mild or moderate intensity, no aggravation by routine physical activity, no nausea/vomiting, no more than one of photo-/phonophobia
Headache associated with intracranial hypertension and hydrocephalus	Ventricular dilation is often observed in Chiari malformation type I	Daily headache, diffuse pain, aggravated by coughing and straining
Low-pressure headache	'Pseudo' Chiari malformation type I, tonsillar descent	Mainly posterior headache, frequently aggravated by cough, dizziness; headache appears or aggravates on standing and disappears in supine position.

Diagnosis

Diagnosis of Chiari malformation type I is based on the patient's history and neurological examination, and confirmed by MRI (Figure 48.1) (19). The International Classification of Headache Disorders, third edition (ICHD-3) helps to identify patients with Chiari malformation type by using operational diagnostic criteria (Box 48.1), including headache characterization, MRI presentation, and evidence of posterior fossa dysfunction. The diagnosis of 'headache attributed to CM' cannot be made until headache resolves within 3 months after treatment of CM.

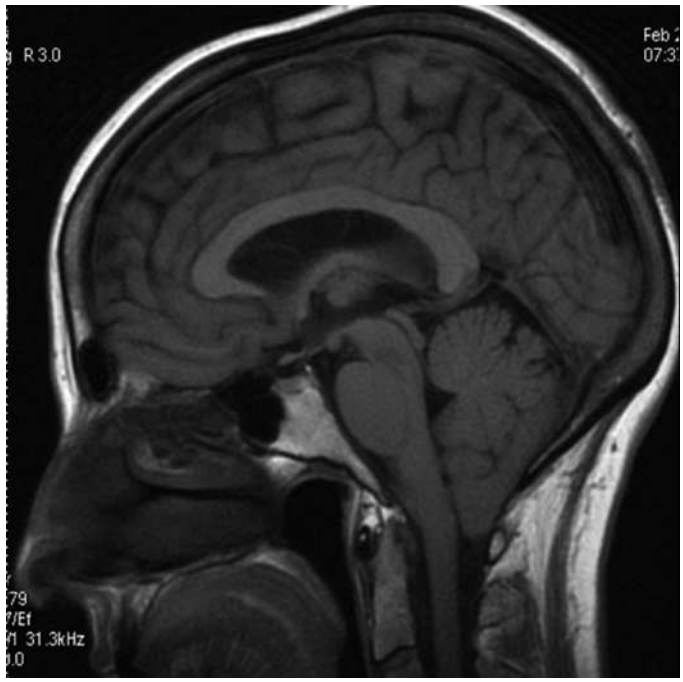

Figure 48.1 Saggital magnetic resonance imaging of a 56-year-old woman meeting criteria for chronic migraine for at least 8 years showing clear tonsillar descent. She had no Valsalva-induced headache and her neurological examination was unremarkable.

Treatment options

In the absence of controlled trials, treatment recommendation is empirical (Figure 48.2). The choice of treatment should be based on the clinical picture and not on the neuro-radiological findings. In asymptomatic patients a conservative non-surgical approach is often warranted. In patients with milder symptoms, symptomatic treatment including analgesics should be offered. Additionally, activities that worsen symptoms, such as heavy lifting, might be avoided. Surgery should only be performed if symptoms reported by the patient are clearly due to CM, are disabling, and persist after conservative treatment. Before considering surgical intervention for treatment of monosymptomatic Chiari malformation type I, primary headache disorders and other symptomatic causes of headache (e.g. intracranial hypotension) should be ruled out. Also, congenital and acquired Chiari malformation type I have to be differentiated before choosing a treatment option (20). In children, aggressive intervention should always take into account days of school missed, days of early dismissal from school, and days of inability to participate in after-school activities (18).

Surgical interventions include decompression, cranioplasty, CSF diversion, and occipital-cervical fusion (21). One study retrospectively analysed the clinical charts of seven patients with Chiari malformation type I younger than 5 years of age, who suffered from headache only (22). All patients were treated with posterior fossa decompression and syringe-subarachnoid shunt when needed. All of these patients reported clinical improvement within 3 months and, after a 6-year period, all remained asymptomatic. However, other studies show that pain may also persist after surgery. Some

Box 48.1 ICHD-3 classification of headache attributed to Chiari malformation type I

Description

Headache caused by Chiari malformation type I (CM1), usually occipital or suboccipital, of short duration (< 5 minutes) and provoked by cough or other Valsalva-like manoeuvres. It remits after the successful treatment of the Chiari malformation.

Diagnostic criteria

A Headache fulfilling criterion C.

B CM1 has been demonstrated.[1]

C Evidence of causation demonstrated by at least two of the following:

- **1** Either or both of the following:
  - (a) Headache has developed in temporal relation to the CM1
  - (b) Headache has resolved within 3 months after successful treatment of the CM1
- **2** Headache has at least one of the following three characteristics:
  - (a) Precipitated by cough or other Valsalva-like maoeuvre
  - (b) Occipital or suboccipital location
  - (c) Lasting < 5 minutes
- **3** Headache is associated with other symptoms and/or clinical signs of brainstem, cerebellar, lower cranial nerve, and/or cervical spinal cord dysfunction.

D Not better accounted for by another ICHD-3 diagnosis.[2]

Notes

[1]Diagnosis of Chiari malformation by MRI requires a 5-mm caudal descent of the cerebellar tonsils or 3-mm caudal descent of the cerebellar tonsils plus crowding of the subarachnoid space at the craniocervical junction as evidenced by compression of the cerebrospinal fluid (CSF) spaces posterior and lateral to the cerebellum, or reduced height of the supraoccipital, or increased slope of the tentorium, or kinking of the medulla oblongata.

[2]Almost all (95%) patients with CM1 report a constellation of five or more distinct symptoms.

[3]Patients with altered CSF pressure, either increased as idiopathic intracranial hypertension or decreased as in spontaneous intracranial hypotension secondary to CSF leak, may demonstrate MRI evidence of secondary tonsillar descent and CM1. These patients may also present with headache related to cough or other Valsalva-like manoeuvre (and are correctly coded as '7.1.1 Headache attributed to to idiopathic intracranial hypertension' or as '7.2.3 Headache attributed to spontaneous intracranial hypotension'. Therefore, in all patients presenting with headache and CM1, CSF leak must be excluded.

Comments:

'7.7 Headache attributed to Chiari malformation type I (CM1)' is often descriptively similar to '4.1 Primary cough headache' with the exception, sometimes, of a longer duration (minutes rather than seconds).

Prevalence studies show tonsillar herniation of at least 5 mm in 0.24–3.6% of the population, with prevalence decreasing in older age. The clinical context of CMI is important as many of these subjects can be asymptomatic. Patients can exhibit 'Chiari-like' symptoms with minimal cerebellar tonsillar herniation, while others may be asymptomatic with large herniations.

These criteria for '7.7 Headache attributed to Chiari malformation type I (CM1)' require validation. Prospective studies with long-term surgical outcome are needed. Meanwhile, rigid adherence to both clinical and radiological criteria is recommended in considering surgical intervention to avoid surgical morbidity. Current data suggest that, in carefully selected patients, cough headaches more than headaches without Valsalva-like precipitants, and occipital headaches more than non-occipital, are responsive to surgical intervention.

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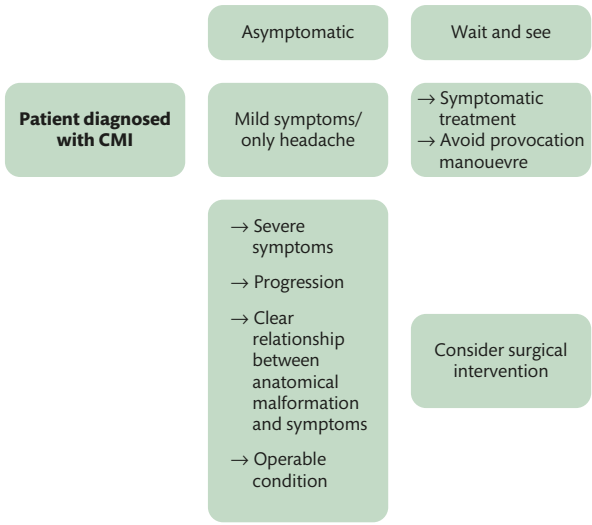

Figure 48.2 Therapeutic algorithm in patients with Chiari malformation type I (CMI).

studies found efficacy of occipital nerve stimulation (ONS) in a subgroup of patients (23–26). A retrospective analysis of 22 patients with Chiari malformation type I with refractory headache after surgery showed that in 86% of patients, ONS led to a significant reduction in pain (25). After ONS implantation, the majority of these patients (n = 13/15) had persistent pain relief (mean follow-up 18.9 months).

Conclusion

Headache is the most common symptom in patients presenting with Chiari malformation type I. Pain is usually localized occipitally and aggravated by Valsalva manoeuvre or physical activity. Diagnosis is based on typical clinical presentation and MRI of the brain. If headache is the only symptom, a therapeutic approach should be taken. In patients where a clear relationship exists between clinical symptoms and the anatomical malformation, and the symptoms are disabling and not responsive to medical therapy, surgical intervention might be considered.

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49

Reversible cerebral vasoconstriction syndrome

Aneesh B. Singhal

Introduction

The term 'reversible cerebral vasoconstriction syndrome' (RCVS) encompasses a group of conditions with similar clinical imaging features, namely segmental narrowing and dilatation of multiple intracerebral arteries (**Figure 49.1**), lasting days to weeks, usually heralded by recurrent thunderclap headaches and often complicated by ischaemic strokes, parenchymal brain haemorrhages, convexal subarachnoid haemorrhages (SAH), or reversible brain oedema (1–7). Arterial pathology, if available, has not shown inflammation or other histological abnormalities (8,9). Unfortunately many patients have been subjected to open brain biopsy and lifelong immunosuppressive treatment due to misinterpretation of this syndrome as a vasculitic disorder. Others have been misdiagnosed as having SAH from ruptured brain aneurysms due to overlapping features such as thunderclap headache and cerebral 'vasospasm'.

RCVS is not a new syndrome. Over the last six decades, approximately 500 cases have been published of patients with the same clinical angiographic features that are now well recognized as RCVS. The onset has been attributed to diverse vasoconstrictive triggers (**Box 49.1**), including prior migraine headache; numerous medications, illicit drugs, and over-the-counter agents that enhance serotonin or nor-epinephrine activity; recent pregnancy; and factors such as high altitude, sexual activity, and neurosurgical procedures (1–6). Accordingly, the nomenclature used to describe such patients has varied, depending largely on the treating clinician's field of expertise: migraine angiitis or migrainous vasospasm (9–11), thunderclap headache with reversible vasospasm (12–14), drug-induced vasoconstriction (15,16), pseudovasculitis (17), benign angiitis of the central nervous system (CNS) (18), eclampsia-associated vasospasm, and postpartum cerebral angiopathy (19). In the field of neurology this entity was considered extremely rare and referred to as Call's or Call–Fleming syndrome based on a case series published in 1988 (20) by a group of authors, including the late C. Miller Fisher, who contributed personal cases collected since 1970 (21).

In 2001, I tentatively proposed the term *cerebral vasoconstriction syndromes* to draw attention to the nearly identical clinical and angiographic features of cases hitherto reported using the aforementioned eponyms (22–25). In 2002, Calabrese's group concluded that their patients previously reported as 'benign angiopathy of the CNS' had vasoconstriction rather than a self-limited inflammatory disorder (26,27). In 2007, Calabrese et al. (1) outlined the key clinical imaging features and differential diagnosis of this syndrome, and suggested that the term *reversible cerebral vasoconstriction syndrome* (RCVS) be applied to subsequent cases in order to increase worldwide recognition. Over the past decade several large cohort studies have been published from USA, Canada, France, and Taiwan (3,6,7,28–36). Today, cases are being routinely diagnosed and published, and RCVS has received its own diagnosis code in the Tenth Edition of the International Classification of Diseases (ICD-10) (167.841). An overlap with posterior reversible encephalopathy syndrome (PRES) and primary thunderclap headache has been recognized, suggesting that these conditions have common elements in their pathogenesis (37,38).

Epidemiology and demographics

Once considered rare, RCVS is being reported with increasing frequency owing to its recent detailed characterization, as well as improved detection of angiographic abnormalities from the widespread use of computed tomography (CT) angiography (CTA) and magnetic resonance angiography (MRA). Some authors believe that its incidence may be increasing as a result of the escalating use of illicit drugs and vasoconstrictive medications that are considered risk factors. The true incidence is not known, but in major academic medical centres, one new patient is seen with this disorder every 3–-5 weeks (2–4,6,7). RCVS appears to affect individuals of all races. Its demographic profile appears remarkably similar across all large cohort studies (2–4,6,7,29,39): the mean age is consistently between 42 and 47 years; men are affected at a significantly younger age than women (mean 35 years vs 44 years) (40); and there is an impressive female preponderance (2:1–9:1), even after accounting for cases related to pregnancy. Cases have been reported in children as young as 8 years and in women up to age 65 years. Women have a higher frequency of migraine and depression, and seem to develop more severe manifestations (40).

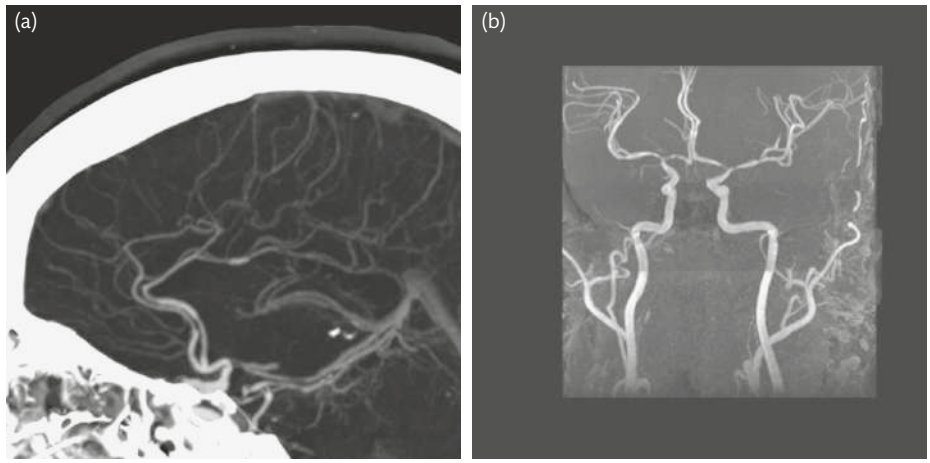

Figure 49.1 Cerebral angiography in reversible cerebral vasoconstriction syndrome (RCVS).

(A) A 55-year-old woman developed a worst-ever, explosive (thunderclap) headache during sexual orgasm. Thunderclap headaches recurred frequently during exertion and bowel movements over the next week. She was on serotonergic antidepressants for depression. Urine toxicology was positive for cocaine. Head computed tomography (CT) angiography (sagittal view, maximum intensity projection images) showed smoothly tapered narrowing and dilatation in multiple intracranial arteries. This 'sausage on a string' appearance is classic for RCVS. (B) A 32-year-old Hispanic man developed recurrent worst-ever, explosive (thunderclap) headaches while lifting weights. Head CT was normal and there was no subarachnoid hemorrhage. Over the next 5 days he developed recurrent thunderclap headaches while exercising. Brain magnetic resonance imaging showed no intracranial lesion. Head magnetic resonance angiography (MRA) showed multifocal segmental narrowing and dilatation, which is typical for RCVS. A follow-up MRA after 2 months showed resolution.

Mechanism

The biological or molecular pathways underlying RCVS have yet to be elucidated. Cerebrospinal fluid (CSF) examination, serological tests, and histopathological studies have ruled out inflammation as a contributing factor (8). Any underlying mechanism should explain not only the recurrent thunderclap headaches that are the major clinical manifestation, but also the segmental and prolonged, yet reversible, nature of the predominantly intracranial angiographic abnormalities, as well as the associated imaging features, such as convexity SAH, reversible brain oedema, ischaemic and haemorrhagic strokes, cervical artery dissection, subdural haemorrhage, and others. At this time the relationship between thunderclap headache and angiographic abnormalities itself is not clear. Of note, 10-15% of patients with RCVS do not report thunderclap headaches (41). Based on serial angiography studies it is clear that headache precedes the arterial changes. Most experts agree that a neurogenic mechanism underlies thunderclap headaches, and that angiographic abnormalities probably indicate an abnormality in the neurogenic control of cerebrovascular tone. The anatomical basis to explain vasoconstriction, as well as the associated headaches, may be the innervation of cerebral blood vessels with sensory afferents from the first division of the trigeminal nerve and dorsal root of C2. Alterations in the function of serotonergic pathways and receptors appear plausible as they are implicated in the pathophysiology of headache and cerebral arterial narrowing, as well as brain oedema. Supporting this theory is the frequent association of RCVS with serotonergic agents (triptans, serotonin and serotonin–norepinephrine reuptake inhibitors, vasoactive tumours, marijuana, liquorice, etc.) and the relatively high incidence of headache disorders and depression both before and after an episode of RCVS. However, many known triggers also have potent sympathomimetic effects, so it is equally possible that an abnormal central sympathetic response induces thunderclap headaches, and that noradrenaline, neuropeptide Y, and other vasoconstrictive factors from sympathetic projections that innervate intracranial arteries are responsible for the segmental arterial calibre changes. The association with pregnancy, ovarian stimulation, and oral contraceptive pills implicates changes in the levels of female reproductive hormones. The diverse range of triggers suggests that multiple pathways may be involved. At the molecular level, several non-hormonal molecular and biological factors (oxidative stress, prostaglandins, endothelial progenitor cells, endothelin, and others)

Box 49.1 Factors associated with reversible cerebral vasoconstrictor syndrome

1. **Headache disorders:** primary thunderclap headache, benign sexual headache, benign exertional headache, migraine.
2. **Changes in oestrogen–progesterone levels:** pregnancy (postpartum angiopathy), ovarian stimulation, oral contraceptive pills.
3. **Vasoconstrictive agents:** triptans, isometheptene, ergotamine tartrate, methergine, selective serotonin reuptake inhibitors, serotonin and norepinephrine reuptake inhibitors, cough and cold suppressants (phenylpropanolamine, pseudoephedrine), diet and energy pills (amphetamine derivatives, Hydroxycut), epinephrine, bromocriptine, lisuride; illicit drugs (cocaine, ecstasy, marijuana, lysergic acid diethylamide); chemotherapeutic drugs (tacrolimus, cyclophosphamide); blood products (red blood cell transfusions, erythropoeitin), intravenous immunoglobulin, interferon-α, nicotine patches, liquorice, ma huang.
4. **Tumours:** phaeochromocytoma, carcinoid tumour, carotid paraganglioma.
5. **Miscellaneous:** hypercalcaemia, porphyria, unruptured saccular cerebral aneurysm, head trauma, spinal subdural haematoma, post-carotid endarterectomy, neurosurgical manipulation of intra-cerebral arteries, tonsillectomy, neck surgery, high altitude, swimming.

have been implicated (42–44). A recent study found a relatively high frequency of vascular abnormalities such as unruptured brain aneurysms, cervical artery dissection, and vascular malformations in RCVS, so an ultrastructural abnormality remains possible (45). The absence of case reports concerning siblings or relatives suggests that there is no genetic predisposition.

Clinical features

The vast majority (85–90%) of patients develop a sudden-onset, excruciating headache that reaches peak intensity within 1 minute, meeting the International Headache Society criteria for thunderclap headache (see also Chapter 34). In the absence of underlying ruptured brain aneurysms or other 'secondary' causes of thunderclap headache (46), these headaches are classified as primary thunderclap headache—unless angiography reveals cerebral vasoconstriction, in which case the term 'headache attributed to RCVS' becomes the more appropriate diagnosis. RCVS onset is frequently associated with sexual activity, cough, exercise, or the application of a cold stimulus, suggesting an overlap with other primary headache disorders within the spectrum of thunderclap headache (e.g. primary cough headache, primary exercise headache, primary headache associated with sexual activity, cold-stimulus headache). The explosive onset with worst-ever pain makes RCVS a dramatic and unforgettable syndrome for the patient and physician alike. Thunderclap headaches can be diffuse or located at the vertex or occiput. They can recur with moderate exertion or the Valsalva manoeuvre for several days, causing a high level of anxiety and distress. An average of 3–4 recurrent thunderclap headaches was observed in one case series; some patients have more than 20 recurrences (3). While some features of thunderclap headache may suggest a diagnosis of migraine (e.g. photophobia, nausea, blurred vision), patients with a history of migraine invariably report that these headaches are quite different from their prior migraine attacks—especially the explosive onset and excruciating intensity of the pain. Severe pain usually subsides within 1–2 hours; however, 50–75% of patients report mild-to-moderate throbbing headache between acute exacerbations. Headache remains the only symptom in many patients. Approximately 10–15% of patients with RCVS develop subacute headache, or are unable to confirm a history of thunderclap headache (2,6,41).

Patients are often agitated upon presentation owing to the severe head pain, and this, in turn, may contribute to hypertension at onset. Data from inpatient cohort studies show that 15–20% develop generalized tonic-clonic seizures at onset (2,6). Recurrent seizures or epilepsy is rare. Large case series show that somewhere between 9% and 63% develop complications such as ischaemic or haemorrhagic strokes or cerebral oedema, with corresponding focal neurological deficits, over a span of 1–2 weeks. Complications rarely develop after the first 2–3 weeks. Visual deficits are common (scotomas, ill-defined blurred vision, hemianopia, cortical blindness, partial or complete Balint syndrome). Symmetric hyper-reflexia and tremor of the outstretched hands are common observations. Other neurological findings include hemiplegia, ataxia, aphasia, and alterations in mental status, as well as coma in patients with large strokes.

Thunderclap headaches subside and clinical deficits usually improve over 2–3 weeks and approximately 85% are able to walk unsupported at the time of hospital discharge. Less severe chronic headache may persist in about 40% of patients. A minority of patients with large infarcts or haemorrhages remain with significant long-term disability. Headaches, clinical deficits, and angiographic abnormalities do not follow a parallel time course of resolution. Typically, thunderclap headaches resolve first, and angiographic resolution occurs by 3 months. Rare patients (2–3%) develop progressive angiographic narrowing that can result in massive strokes and death.

Blood and serological tests

As discussed in the next section, RCVS is a clinical imaging diagnosis (2); laboratory tests are not indicated except to rule out serious underlying conditions or mimics in rare cases. For example, urine vanillylmandelic acid and 5-hydroxyindoleacetic acid may be considered to rule out phaeochromocytoma (17), and infectious disease and rheumatology panel tests, as well as CSF examination, may be indicated to rule out secondary causes of thunderclap headache (e.g. meningitis) or angiographic abnormalities (e.g. infectious arteritis). Serum and urine toxicology screens are useful to investigate for triggers such as marijuana and cocaine. There is no role for brain biopsy or temporal artery biopsy in patients with typical features of RCVS (2).

Brain and vascular imaging

In any patient with thunderclap headache it is imperative to proceed urgently with brain and vascular imaging to exclude secondary causes such as ruptured brain aneurysms, cerebral venous sinus thrombosis, cervical artery dissection, posterior cerebral or middle cerebral artery embolism, intracerebral haemorrhage, and meningitis (46). Approximately 30–70% of patients with RCVS are reported to have normal brain scans upon admission, even though the cerebral arteries may show severe multifocal vasoconstriction. Follow-up head CT or brain magnetic resonance imaging (MRI), often performed to evaluate recurrent headaches or new focal deficits, show that 80% of patients ultimately develop lesions, including small convexity (non-aneurysmal) SAHs, ischaemic strokes, parenchymal haemorrhages, reversible brain oedema, and, rarely, subdural haemorrhage (**Figure 49.2**). Any lesion combination can be present. Indeed, in a patient with thunderclap headache, the evolution from normal to abnormal scan findings within a period of few days is distinctive for RCVS.

The topography of ischaemic strokes is notable. The diffuse arterial involvement results in bilateral, symmetric ischemic lesions that involve the watershed regions of the anterior, middle, and posterior cerebral arteries, or the superior and posterior inferior cerebellar arteries. In many patients the cortical–subcortical junctions are first affected, presumably because these regions form the borderzone between superficial and deep arteries. Cerebral perfusion imaging, if performed, reveals hypoperfusion in similar arterial watershed locations.

Approximately one-third of patients develop vasogenic oedematous lesions in the cerebral or cerebellar hemispheres, best appreciated on fluid-attenuated inversion recovery (FLAIR) MRI. These

lesions disappear within days to weeks and resemble the lesions described in PRES, suggesting a shared pathophysiology between RCVS and PRES (8,47,48). Infrequently, infarcts or haemorrhagic conversion have been observed within the regions of oedema (49), implicating distal vessel vasoconstriction and vasodilatation, as well as endothelial dysfunction as the underlying mechanism.

SAHs are documented in more than one-third of admitted patients (30,50). Unlike the typical sylvian fissure or basal location of aneurysmal subarachnoid haemorrhage, in RCVS the SAHs overlie hemispheric convexities and are small, occupying no more than 2–3 sulcal spaces (34,51). Multiple convexity SAHs can occur simultaneously. They are best appreciated on FLAIR MRI; however, correlation with head CT and susceptibility-weighted MRI is needed to distinguish convexity haemorrhages from proteinaceous fluid exudation, as well as dilated cortical surface arteries, which appear as dot- or linear-shaped hyperintensities deep within sulcal spaces (39,52). Recent studies suggest that RCVS is the most frequent cause of convexity SAH in individuals younger than 60 years of age (53).

Parenchymal haemorrhages are typically lobar, less frequently located in the deep grey nuclei, and can be multiple in number (30,50,54,55). Indeed, RCVS is one of the few conditions associated with multiple simultaneous brain haemorrhages (56). The location of haemorrhages is similar to that of infarcts, supporting ischemia–reperfusion injury as the underlying mechanism. Subdural haemorrhages are reported in rare cases (30,50). Haemorrhagic lesions tend to occur early (within the first week) with parenchymal haemorrhages occurring earlier than SAHs. Infarcts and oedema accumulate later, but rarely after 2 weeks. Patients with these complications have more severe vasoconstriction than those with normal scans. Triggers and risk factors do not predict lesion subtype; however, women seem to have a higher risk of haemorrhage (50).

The main diagnostic feature of RCVS is multifocal areas of smooth tapering cerebral artery narrowing and dilatation ('sausage on a string' appearance; **Figure 49.1**). Historically, this appearance has been attributed to cerebral vasculitis; however, most patients with the latter condition have an irregular, notched appearance of cerebral arteries, as can be expected from an inflammatory process (2). Angiographic abnormalities in RCVS can be documented using trans-femoral angiography, CTA or MRA (**Figure 49.2**), with the latter two modalities being preferred owing to lower risk. Large studies have shown that the cerebral vasoconstriction starts distally and progresses proximally (2,3,29,30,50). Therefore, initially normal angiography does not exclude RCVS in patients with otherwise consistent clinical and brain imaging features. A follow-up vascular imaging study may be justified after an interval of 3–8 days to 'confirm' this diagnosis. Transcranial Doppler ultrasound can show elevated blood flow velocities (19,28,57,58), but many patients have normal blood flow velocities despite the presence of diffuse vasoconstriction. Hence, this modality has greater utility in monitoring angiographic evolution. Transcranial Doppler ultrasound studies have shown abnormal cerebral vasoreactivity (reduced breath holding index), reflecting the altered cerebral vascular tone that underlies RCVS (59). The time course of vasoconstriction is variable, but most patients show resolution within 3 months.

Cervical artery dissection has been documented in many patients with RCVS (37,60–62). In one study, dissections were found in 12% of patients with RCVS and RCVS was documented in 7% of patients with dissection (63). Cervical artery dissection in RCVS may result from the dynamic changes in arterial calibre, or acute hypertension, or another mechanism. A recent study (45) found a high frequency of concurrent vascular abnormalities (cervical artery dissection, unruptured cerebral aneurysms, cavernous malformations, fibromuscular dysplasia) in RCVS, the significance of which is uncertain.

Approach to diagnosis

The recent characterization of the clinical, imaging and angiographic features of RCVS (1–7), including its distinction from historic mimics such as primary angiitis of the central nervous system (PACNS) (2,33) (see also Chapter 46) and aneurysmal SAH (34) (see also Chapter 34), has made it possible to accurately diagnose RCVS upon initial clinical presentation using only clinical and brain imaging features. For example, the presence of recurrent thunderclap headaches is pathognomonic for RCVS (2). However, the

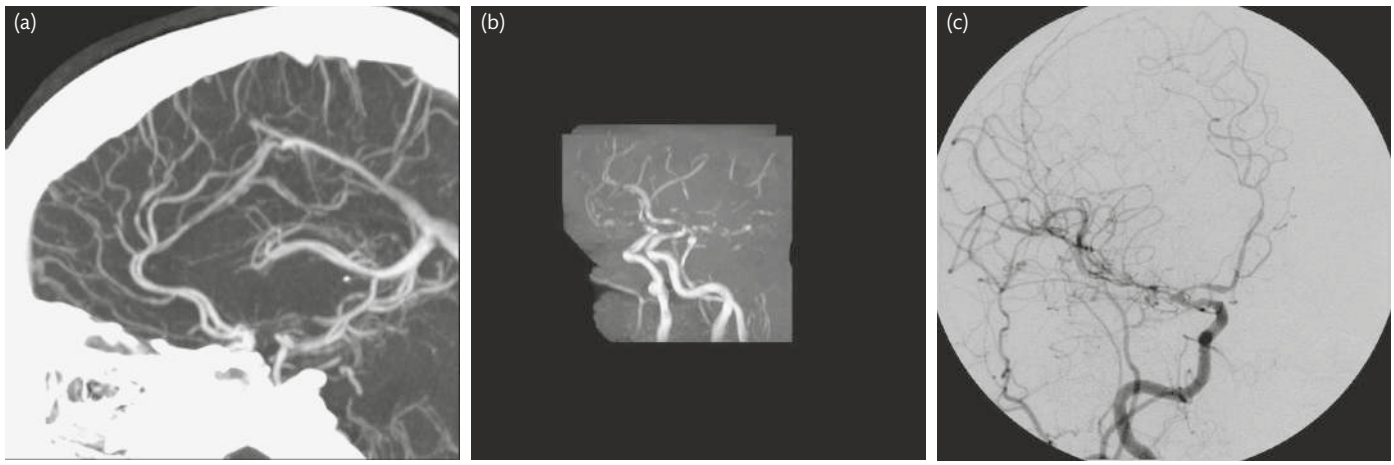

Figure 49.2. Comparison of cerebral angiographic modalities in reversible cerebral vasoconstriction syndrome (RCVS).

(A) Computed tomography angiography, (B) magnetic resonance angiography, and (C) digital subtraction angiography show segmental narrowing and dilatation of multiple intracranial arteries in a 44-year-old woman with RCVS.

individual clinical and imaging features have a broad differential diagnosis.

As stated earlier, in patients presenting with thunderclap headache, it is critical to immediately exclude other causes (aneurysm rupture, cerebral venous sinus thrombosis, etc.) with appropriate brain and vascular imaging, and sometimes CSF examination (46). Aneurysmal rupture is a major consideration because these patients can also have thunderclap headaches, subarachnoid blood, and cerebral vasospasm (see also Chapter 34). However, the recurrent nature of thunderclap headaches, the convexity/sulcal location and small quantity of subarachnoid blood, and the widespread, symmetric vasoconstriction distinguish RCVS from aneurysmal SAH (34). Once these potentially serious entities are excluded, the patient can be diagnosed with primary thunderclap headache—or RCVS, if cerebral angiography shows segmental multifocal narrowing (38).

A common mistake is to attribute the onset headache to underlying migraine and treat patients with antimigraine agents or glucocorticoids, which can cause further disease progression (23,55,64). Migraine is often considered because many patients with RCVS report a prior history of migraine, the symptoms (severe headache, photophobia, nausea, emesis) may overlap with symptoms of migraine, the thunderclap nature of the onset is not appreciated, posterior watershed infarcts resemble the lesions of migraine-induced stroke, and because migraine headache has been associated with cerebral angiographic abnormalities (65–75). Indeed, some authors believe that RCVS is simply the fortuitous documentation of vasoconstriction in a severe migraine attack (76). However, there are important differences between RCVS and migraine. Although reversible, the angiographic abnormalities of RCVS usually persist for days to weeks, whereas most patients with migraine have normal angiography results. The presenting headache in RCVS is explosive, without any accompanying premonitory or aura symptoms. Migraine is rarely, if ever, explosive with maximal intensity at onset or within 60 seconds. Unlike RCVS, migraine is a recurrent disorder, has a primarily neuronal basis, and has genetic implications.

On imaging, the presence of infarcts or haemorrhagic lesions may raise the possibility of other causes of stroke in the young. It is important to note that RCVS is one of the few conditions with multiple lesion types occurring simultaneously (e.g. SAH or arterial dissection along with multifocal infarcts and vasogenic oedema). Further, the brain imaging evolution from normal to abnormal within days, and the typical lesion topography, provides clues to the diagnosis (**Figure 49.3**). Lastly, in isolation, cerebral angiographic abnormalities can raise concern for pathological entities such as atherosclerosis, infections, vasculitis, moyamoya disease, fibromuscular dysplasia, and other cerebral arteriopathies (see also Chapters 10, 37, and 46). These can be excluded by a careful medical history and appropriate laboratory tests.

There are no validated criteria for diagnosis. The key clinical and angiographic features, summarized over a decade ago (1,22), include recurrent severe thunderclap headaches and multifocal intracranial arterial narrowing and dilatation, in the absence of a ruptured cerebral aneurysm and without evidence for mimics such as cerebral vasculitis. Historically, distinction from PACNS has been challenging because headache, stroke, seizures, and angiographic irregularities are common to both conditions (65). While there is overlap, the nature of the headaches and imaging abnormalities, and the onset and tempo of the diseases, are substantially different. In a recent study comparing the features of 159 patients with RCVS to 47 patients with PACNS (2), it was shown that recurrent thunderclap headaches have a 98% specificity and a 99% positive predictive value (PPV) in diagnosing RCVS and distinguishing it from PACNS (which has a slower course, with insidious dull headaches). Further, it was shown that RCVS can be diagnosed in patients with a single thunderclap headache with 100% specificity and 100% positive predictive value if brain imaging is normal, or shows watershed-only infarcts (unlike the small deep infarcts in PACNS), or vasogenic oedematous lesions. In patients without thunderclap headache who have abnormal angiography, the absence of brain lesions virtually rules out PACNS. It should be noted that severe and prolonged vasoconstriction can rarely culminate in secondary inflammation, rendering the angiographic changes irreversible. This phenomenon, mostly associated with highly potent sympathomimetic drugs, can blur the distinction between RCVS and PACNS (56,77). In cases where clinical imaging features prove insufficient for the diagnosis, high-resolution contrast-enhanced vessel-wall MRI is being investigated as a potential tool for diagnosis (78).

Management

It is important to first exclude secondary causes of thunderclap headache, and then focus on a prompt and accurate diagnosis using the approach described earlier. Once the diagnosis is suspected or secured, it is logical to remove the potential trigger (e.g. vasoconstrictive medication), and start symptomatic treatment for the severe head pain and agitation. The guiding management principal is 'less is more', as RCVS is usually a self-limited syndrome with excellent outcome. Treatment of headache with triptans or other vasoconstrictive agents should be avoided. Patients should be counselled to avoid physical exertion, the Valsalva manoeuvre, and other known triggers of recurrent headaches for a several weeks to 1 month. Stool softeners are advocated to minimize the Valsalva manoeuvre (79). The role of pharmacological blood pressure manipulation is uncertain. Raising the blood pressure runs the risk of worsening vasoconstriction, and lowering it can compromise cerebral perfusion. Acute seizures may warrant treatment; however, long-term seizure prophylaxis is not warranted. The usual stroke preventive medications, such as antiplatelets, anticoagulants, and cholesterol-lowering agents, are not indicated (5,79).

The known evolution of complications over 1–2 weeks makes it reasonable to admit patients for observation for a few days, at least until resolution of recurrent thunderclap headaches. In one study, the risk for clinical worsening was high in patients with early ischaemic stroke, prior hypertension and depression, and use of serotonergic antidepressants, and low in patients with convexity SAH and normal admission brain imaging findings (80). These data may influence discharge planning. While one-third of patients can develop new deficits in the first 2–3 days (7), these deficits are often transient and do not warrant intervention unless the patient develops progressive neurological deficits. Given the usually benign natural history, substantial clinical experience is required to judge the appropriate threshold for intervention. Calcium channel blockers (oral nimodipine and verapamil, intravenous magnesium) have not been shown to relieve vasoconstriction but may relieve the intensity of headache. Provided the symptoms have

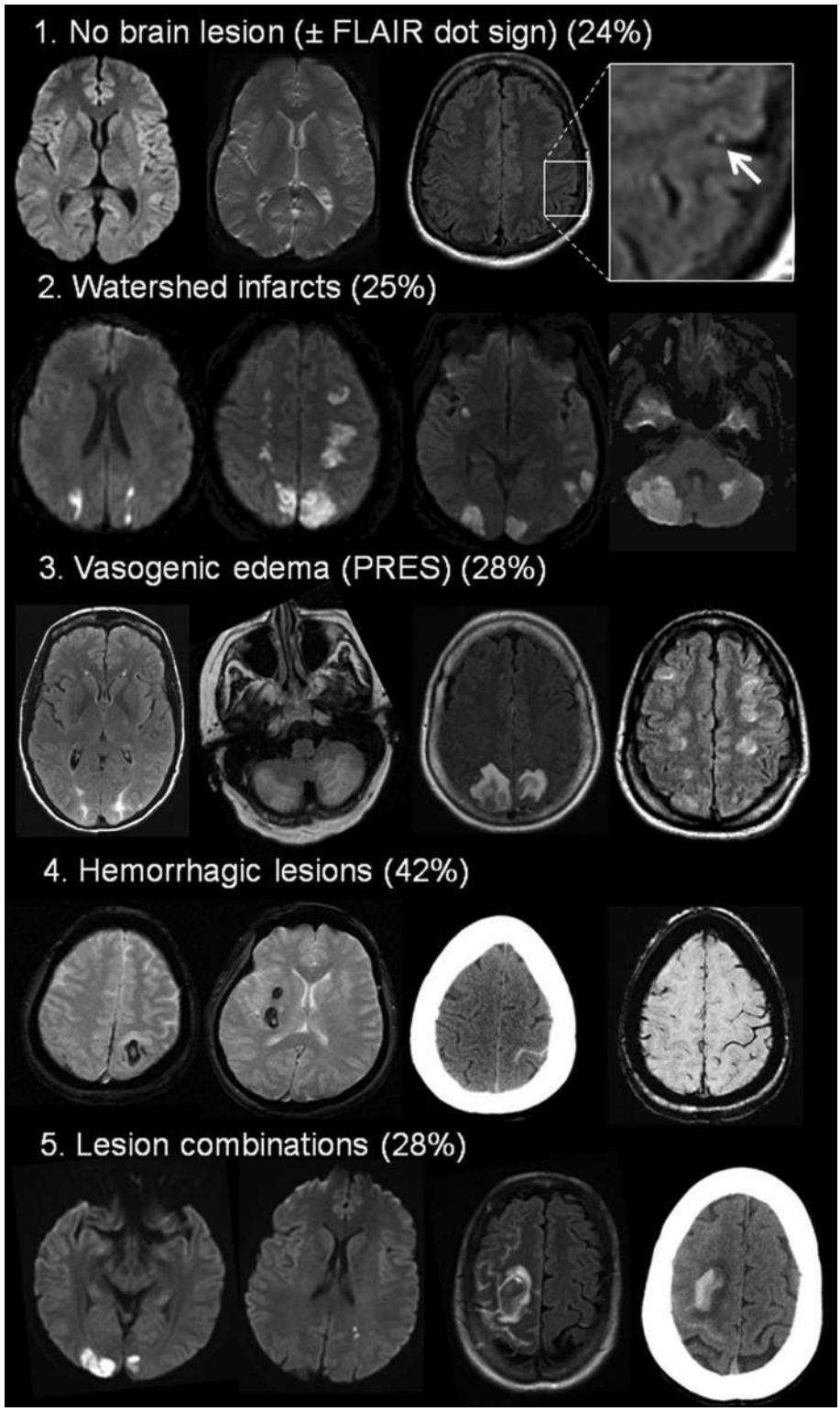
1. No brain lesion (± FLAIR dot sign) (24%)
2. Watershed infarcts (25%)
3. Vasogenic edema (PRES) (28%)
4. Hemorrhagic lesions (42%)
5. Lesion combinations (28%)

Figure 49.3 Brain lesions in reversible cerebral vasoconstriction syndrome (RCVS).

Representative brain images from patients with RCVS are shown to highlight different lesion patterns. The numbers in parentheses show the percentages of the lesion patterns (totals exceed 100% owing to lesion combinations). Pattern 1, no acute parenchymal lesion. Normal axial diffusion-weighted (DWI), gradient echo (GRE), and fluid-attenuated inversion recovery (FLAIR) images. The hyperintense dot sign is present on FLAIR (far right, arrow). Pattern 2, borderzone/watershed infarcts. Far left, DWI showing typical symmetric, posterior infarcts that spare the cortical ribbon. Middle and far right, DWI shows widespread watershed infarcts. Pattern 3, vasogenic oedema. Subcortical crescent-shaped T2-hyperintense lesions consistent with posterior reversible encephalopathy syndrome on FLAIR. Pattern 4, haemorrhagic lesions. The two left images (axial GRE) show simultaneous lobar and deep intra-parenchymal haemorrhages. The two right images show convexal subarachnoid haemorhages on computed tomography (CT) and axial GRE. Pattern 5, lesion combinations. The two images on the left show bilateral watershed infarcts on DWI and the two on the right show lobar, as well as convexal, subarachnoid haemorrhages on axial FLAIR and CT, all in the same patient.

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resolved and no complications have occurred, these medications can be discontinued 1 month after the onset of symptoms or after angiographic resolution of the vasoconstrictive changes has been documented. Glucocorticoid therapy is associated with significant persistent clinical worsening, new brain lesions, angiographic progression, and worse discharge clinical outcomes (80). An example case is presented in Figure 49.4. Hence, the widely deployed strategy of starting empiric glucocorticoid therapy while awaiting the final diagnosis or 'until PACNS is excluded' is no longer justified. Intra-arterial vasodilator infusions can induce prompt resolution of angiographic vasoconstriction. For this reason, intra-arterial vasodilators are being advocated as a diagnostic tool to exclude mimics

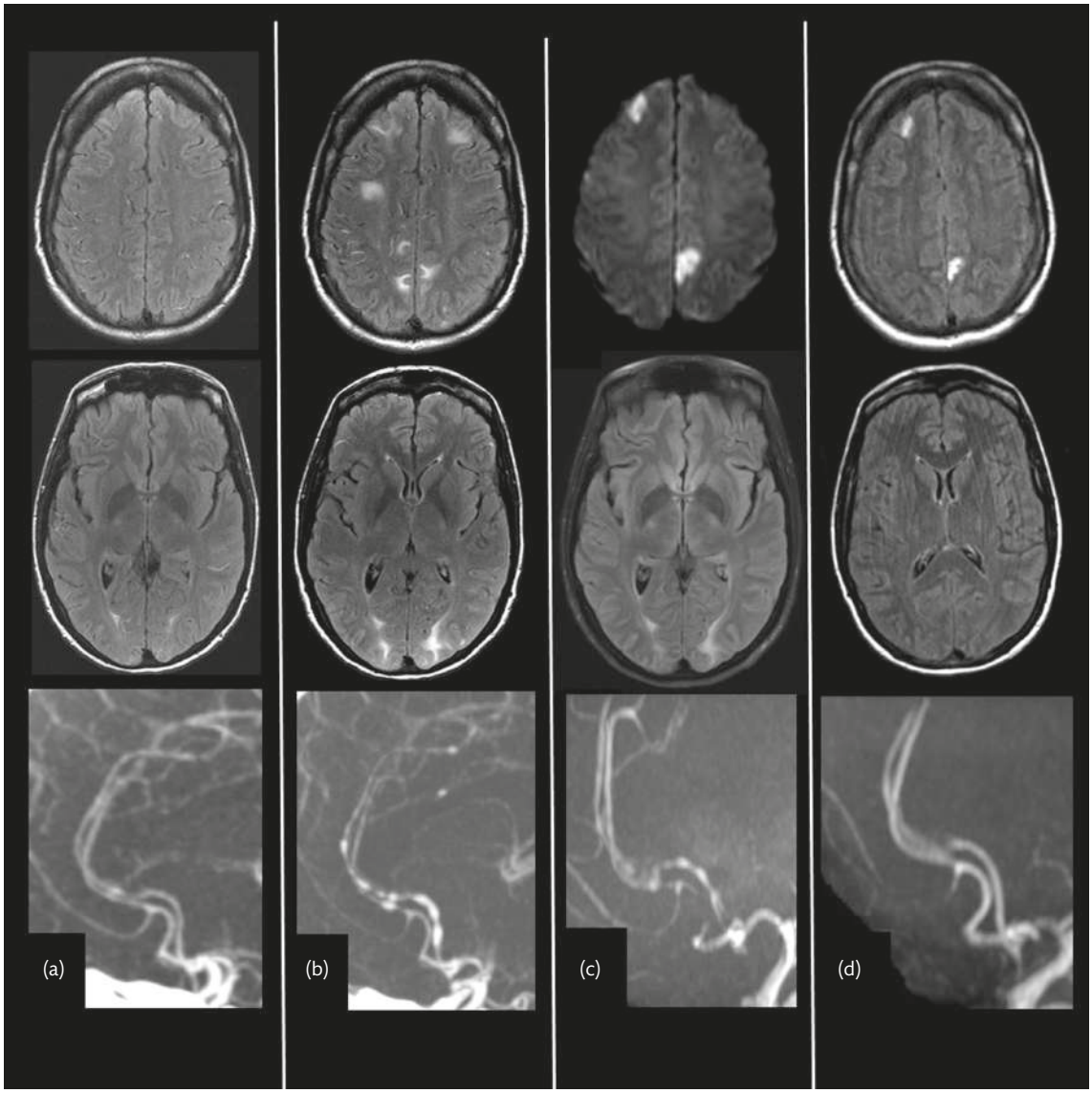

Figure 49.4 Glucocorticoid-associated clinical, radiological and angiographic worsening in reversible cerebral vasoconstriction syndrome (RCVS).

A 43-year-old woman with malabsorption syndrome, on parental nutrition, was hospitalized for treatment of port-a-catheter infection. On day 2 she developed a thunderclap headache. Head computed tomography (CT) and cerebrospinal fluid examination were normal. Hydrocortisone 100 mg q8h was administered for suspected adrenal insufficiency and sepsis. On day 4, brain magnetic resonance fluid-attenuated inversion recovery (FLAIR) images showed multiple dot- and linear-shaped sulcal hyperintensities, suggesting dilated cortical surface arteries (A, top), and subtle bilateral white matter vasogenic edematous lesions (A, middle) consistent with posterior reversible encephalopathy syndrome (PRES). Headaches recurred, and on day 7 she developed cortical blindness. Head CT angiography (CTA; A, bottom) showed segmental narrowing of multiple intracranial arteries. Brain magnetic resonance imaging (MRI) showed new PRES lesions and progression of prior PRES lesions (B, top and middle). She was transferred to the author's hospital. Neurological examination showed features of the Balint syndrome and aphasia. Repeat CTA showed worsening cerebral vasoconstriction (B, bottom). Hydrocortisone was tapered to 25 mg q12h; nimodipine and magnesium were administered for suspected RCVS. Repeat MRI on day 9 showed new bilateral ischaemic lesions on diffusion-weighted images (C, top), persistent PRES (C, middle), and stable cerebral vasoconstriction (C, bottom). The port-a-catheter infection was successfully treated. She was discharged on dDay 19 on oral prednisone 5 mg daily and nimodipine. Follow-up imaging on day 42 showed established infarctions on FLAIR images (D, top), reversal of PRES lesions (D, middle), and resolution of vasoconstriction (D, bottom). Neurological examination showed no residual deficits.

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such as atherosclerosis or vasculitis where a robust vasodilator response would be unexpected (81,82). Keeping in mind the profound risks of this invasive procedure (including rebound vasoconstriction and reperfusion injury) (8), and the high accuracy of recently published diagnostic criteria (2), this approach cannot be justified for diagnostic purposes. In addition, given variable outcomes with this strategy (8,83), it should be reserved only for patients showing clear clinical progression from relentless vasoconstriction despite best medical management.

Patients should be reassured that, at present, their long-term outcome appears excellent (36). Follow-up studies show that recurrent thunderclap headaches can occur in approximately 11% of patients (35). However, an episode of RCVS with recurrent thunderclap headaches and ensuing complications is extremely rare. Some patients develop chronic headaches and depression; nevertheless, illicit drugs and vasoconstrictive medications should be avoided if clinically feasible. Triptans and other vasoconstrictive antimigraine agents are best avoided in patients with migraine, especially if they develop stroke. For patients with depression who require treatment, it is advisable to start with less vasoconstrictive antidepressants (amitriptyline, bupropion). It should, however, be noted that some patients have been re-exposed to serotonergic drugs such as triptans and selective serotonin reuptake inhibitors without recurrence of RCVS. Genetic counselling does not appear necessary. The future risk of RCVS or PRES in pregnant women is uncertain, but it is advisable to monitor and promptly treat hypertension, proteinuria, and other signs of pregnancy-induced hypertension. Future studies are still required to clarify mechanisms and provide epidemiological information about medication risks and long-term implications of RCVS.

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PART 7
Special topics

50. **Headaches in the young** *459*
Vincenzo Guidetti, Benedetti Bellini, and Andrew D. Hershey

51. **Headaches in the elderly** *470*
Jonathan H. Smith, Andreas Straube, and Jerry W. Swanson

52. **Headache and psychiatry** *475*
Maurizio Pompili, Dorian A. Lamis, Frank Andrasik, and Paolo Martelletti

53. **Headache and hormones, including pregnancy and breastfeeding** *484*
Sieneke Labruijere, Khatera Ibrahimi, Emile G.M. Couturier, and Antoinette Maassen van den Brink

54. **Headache and the weather** *494*
Guus G. Schoonman, Jan Hoffmann, and Werner J. Becker

55. **Headache and sport** *502*
David P. Kernick and Peter J. Goadsby

56. **Headache attributed to airplane travel** *508*
Federico Mainardi and Giorgio Zanchin

57. **Headache and sleep** *514*
Stefan Evers and Rigmor Jensen

58. **Headache and fibromyalgia** *523*
Marina de Tommaso and Vittorio Sciruicchio

59. **Visual snow** *530*
Gerrit L.J. Onderwater and Michel D. Ferrari

50

Headaches in the young

Vincenzo Guidetti, Benedetti Bellini, and Andrew D. Hershey

Introduction

Recurrent headaches are a common health complaint for children and adolescents. When these headaches recur and are brought to medical attention, they are more frequently noted to be migraine, but there are also a significant number of patients with tension-type headache (TTH). The pathophysiology, characteristics, and response to treatment for children and adolescents can be considered to be similar to adults, with unique aspects that correlate to the developmental level of the children and the progression of their disease.

Diagnosis and criteria

The diagnosis and characterization of headaches in children has evolved over the centuries. Tissot (1), Calmeil (2), and Liveing (3) referred to childhood headaches in their discussion of migraines (summarized in (4)), but their reference to childhood headache was limited to the observation that migraines may start in childhood. Initial descriptions of the whole spectrum of childhood headaches appeared in the early 1900s (5–9). These investigations identified that children could suffer from the same headache disorders as adults, albeit with subtle variations.

In 1949, Vahlquist and Hackzell (10) began a much more extensive study of childhood headaches. They reported their findings from 31 patients with onset of headache between 1 and 4 years of age and developed criteria for childhood migraines. Differences they noted between children and adults were a predominance of male patients in children, shorter duration of headaches in children, temperature changes during headache in children, and a psychogenic element in more children. One of the most significant features of their study and subsequent work was the initial establishment of criteria for the diagnosis of childhood headaches. These criteria described paroxysmal headaches that included two of four features: pain limited to a part of the head, the presence of nausea, the presence of a flicker scotoma, and a positive family history. In 1955, Vahlquist, in collaboration with Bille, Ekstrand, and Hackzell, used these initial criteria to screen 1236 schoolchildren between the ages of 10 and 12 years for the presence of migraine (described in (4)). They found a prevalence of 4.5%, while the prevalence of non-migrainous headaches was 13.3%.

Bille later expanded on this study in his very thorough work on headache in children (4). Questionnaires were distributed to 9059 school children in Uppsala, Sweden, aged 7–15 years old in 1955 (with a remarkable 99.3% response rate). The children and their parents were asked about the presence of headaches and, if headaches were present, they were asked to describe its features. The children were then divided into four groups: (i) children who never had a headache (n = 3720; 41.1%); (ii) children with rare non-paroxysmal headaches (n = 4316; 48.0%); (iii) children with frequent non-paroxysmal headaches (n = 473; 5.3%); and (iv) children with paroxysmal headaches (n = 484; 5.4%), i.e. migraine. The most frequently reported features in this last group were one-sided pain, nausea, visual aura, and a positive family history. From this study, Bille identified that by the age of 5 years, approximately 25% of children reported a significant headache, and by the age of 15 years, 75% of children had reported a significant headache. Within this age range Bille was able to demonstrate a prevalence range for migraines from 1% to 7%, dependent on age and sex. To more accurately assess the headache diagnosis, he contacted every fifth child in the 'migraine' group and every tenth child in the non-migrainous paroxysmal group, and was able to estimate the prevalence of migraine to be 3.97% (n = 357/8993). He also discovered a lack of differences in these children versus their headache-free counterparts in school performance, school attendance, and socio-economic status. He further described the characteristics of these children and their headaches, including detailed features of the headaches, paediatric and neurological examinations, and electroencephalography (EEG) examination. Subsequently, he followed 73 children in the migraine group for up to 40 years (11). Of these, 23% were migraine free by the age of 25 years; however, more than half continued to have migraine at the age of 50 years.

In 1976, Prensky reviewed the differences in children's migraines versus adult migraine (12). In children there was a slight predominance of males (–60% vs –33%), less likelihood of a unilateral headache (25–66% vs 75–91%), more nausea/vomiting (70–100% vs 60–90%), less visual aura (10–50% vs 60–75%), and an increased incidence of seizures (5.4–12.3% vs < 3%). He also noted that the familial incidence was approximately the same (72% vs 71%).

In 1984, Barlow gave a descriptive account on childhood migraine (13). Much information was based on personal observations on 300 children with headaches over a 20-year period. Through

these observations, as well as a review of the literature, he focused on his experience with managing childhood headaches and also the problems that arose. This included not only migraine, but also migraine variants, periodic syndromes, psychogenic headaches, traumatic headaches, symptomatic headaches, and various treatment designs. He reported that family history for migraine is a factor in approximately 90% of paediatric cases and that environmental and biological events exist that precipitate migraine episodes, such as fatigue, psychological stress, physical exertion, and hormonal factors.

In 1988, the first edition of the International Classification of Headache Disorders (ICHD) was released (14), followed by the second edition in 2004 (15) and, more recently, the third edition in 2013 (16). The ICHD is now established as the scientific foundation for the diagnosis of headaches for research studies and can be used as a tool for the clinical diagnosis of headaches. For children, there has been special recognition of the unique characteristics to assist with the diagnosis of headaches. Many of these characteristics evolve into the more typical adult pattern as children grow up to adulthood. Some of these observations include the recognition that children's headaches may be shorter in duration, more likely to be bilateral (especially frontal), the potential difficulty of children expressing the associated symptoms of photophobia and phonophobia, and the potential usefulness of drawings in the establishing a diagnosis. In fact, children tend to communicate their symptoms more effectively through drawings than verbally. The 'artistic diagnosis' is accurate in predicting the 'clinical diagnosis' of migraine, with a sensitivity of 69.6%, a specificity of 88%, a positive predictive value (PPV) of 84.2%, and negative predictive value of 75.9 (17,18).

Although the ICHD-3 diagnosis has a high sensitivity, there are still some limitations. The ICHD-3 diagnosis of migraine is more sensitive and accurate with a prospective diary analysis in children than a retrospective analysis. In the 25 years that elapsed between ICHD-1 and ICHD-3, classification of migraine episodes lasting < 2 hours were acceptable when associated with information from a diary. The current ICHD-3 classification does improve and advance migraine diagnosis in children and adolescents; however, more research is needed on other characteristics of headache to focus on developing criteria in this age group that are distinct from those applicable to adults (19).

Epidemiology

Headache is the most common somatic complaint in children and adolescents, based on multiple clinical and epidemiological databases. The incidence of childhood migraine and other frequent headaches appears to have substantially increased over the last 30 years (20,21), although this may be because of more extensive attention to the problem and more accurate diagnostic criteria. The reported prevalence of headache in schoolchildren varies greatly among studies, from 5.9% to 82%, depending on the definition criteria (22). The vast majority of those headaches are primary headache disorders that can be classified as migraine or TTH. By 3 years of age, headache occurs in 3–8% of children (23). At 5 years of age, 19.5% have headache and by 7 years of age, 37–51.5% have headache (24). In 7–15-year-olds, headache prevalence ranges from 26% to 82% (25). A comprehensive review of population-based studies of headache in children and adolescents summarized evidence from 50 studies of young people under the age of 20 years (26). The aggregate prevalence of headaches was 58.4%, and that of migraine 7.7%. The weighted 12-month prevalence rate was 10.1%, and lifetime prevalence 12.9%. The prevalence increased with age from 6.1% in children under the age of 13 years to 7.8% in adolescents. Several studies of children also provided information on migraine with aura, the weighted prevalence of which among those under age 18 years of age was 1.6% (27). A review by Wöber-Bingöl (28) covers epidemiological studies on migraine and headache in children and adolescents published in the past 25 years. A total of 64 cross-sectional studies have been identified, published in 32 different countries, and including a total of 227,249 subjects. The estimated overall mean prevalence of headache was 54.4 % (95% confidence interval (CI) 43.1–65.8) and the overall mean prevalence of migraine was 9.1 % (95% CI 7.1–11.1).

Migraine affects males and females equally at an age of 14 years and younger, but more females than males have migraine in adolescence and young adulthood (26). Abu-Arafeh et al. (26) reported on statistically significant differences in the prevalence of migraine between Europe and the Middle East on the one hand, and the USA and the Far East on the other. The prevalence in Europe is 8.35, in the Middle East it is 8.69, in the Far East it is 6.70, and in the USA it is 6.58. The differences are probably a combination of genetic predisposition, as well as environmental factors. Despite the clear differences in migraine prevalence in different regions of the world, it is not possible to assume that the differences are due to racial background, as most studies did not provide data on the racial make-up of their populations.

Childhood periodic syndromes

Childhood periodic syndromes or 'episodic syndromes that may be associated with migraine' (in the parlance of ICHD-3) are a diverse group of disorders that predominantly occur in children but in some cases can also occur in adults: infant colic, benign paroxysmal torticollis, benign paroxysmal vertigo, abdominal migraine, and cyclical vomiting. Some children will evolve from one periodic syndrome into another with age (29,30). These syndromes are thought to be early-life manifestations of those genes that later in life are expressed as migraine headache. For example, benign paroxysmal torticollis has been linked to the familial hemiplegic migraine gene *CACNA1A* (31).

Recognizing and understanding childhood periodic syndromes is important for several reasons. Firstly, children with these disorders often undergo extensive and sometimes invasive medical testing. Recognizing their disorders as migrainous could spare them such testing. Of course, appropriate treatment for these disorders first requires a correct diagnosis. Hearing about a history of a periodic syndrome might help a clinician to diagnose migraine headache in a child or adolescent down the line.

Infant colic

Infant colic, or excessive crying in an otherwise healthy and well-fed infant, occurs in 5–19% of infants (32). Infant crying peaks at 5–6 weeks of life and declines by 3–4 months of age (33). Colic is an amplified version of this developmental crying pattern. Definitions of infant colic vary, but one of the most commonly used is Wessel's

criteria of crying for at least 3 hours a day, at least 3 days a week, for at least 3 weeks (34). Despite much research over the nearly 60 years since Wessel's initial 1954 description of infant colic, we have not made significant progress in understanding its aetiology or in finding an effective therapy. Therapies that reduce infant crying could ease caregivers' frustration and protect infants from harm.

An association between infant colic and childhood migraine has been reported in several retrospective case–control studies (35–37). In a cross-sectional study, mothers with migraine were more than twice as likely to have an infant with colic (38). In a meta-analysis study, the odds of migraine were increased 5–6-fold if there was a history of infant colic (36). In a prospective cohort study, 'hyperreactivity' in early infancy, with crying being one of the factors incorporated into this concept, was a predictor of migraine in childhood (39).

Most convincingly, in a recent population-based prospective cohort study, infant colic was associated with an increased risk of developing migraine without aura by 18 years of age, but not migraine with aura (40), suggesting that certain migraine genes might lead to specific clinical migraine phenotypes. If infant colic is a migrainous phenomenon, it could provide a neurodevelopmental explanation for many of colic's characteristics, for example, the fact that colicky crying develops at several weeks of life. Migraineurs experience increased sensitivity to stimuli (41), and infants' perceptual abilities are rapidly increasing during the first weeks of life. It is possible that infants with colic have migraine genes that make them more sensitive to stimuli and they express that through increased crying. Similarly, increased sensitivity to stimuli could explain why colicky crying tends to happen in the evenings, as that is when infants are at the end of a long day of stimulation, or as with migraine there may be an influence of circadian biology. Alternatively it is possible that the association between infant colic and migraine is due to a shared genetic predisposition to both disorders, rather than infant colic being an early-life expression of migraine genetics per se. If infant colic is a migrainous phenomenon, it could also help explain why colic resolves around the age of 3 months. Three months of age is approximately when the infant brain develops rhythmic excretion of endogenous melatonin (42) and night-time sleep consolidation (43). The ability of sleep to help terminate migraine attacks, particularly in young children, is well recognized. Poor sleep can also trigger childhood migraine attacks (44). Developing rhythmic endogenous melatonin excretion and a predictable sleep pattern could help extinguish an age-sensitive manifestation of migraine-like colic (43). An open-label study suggested that melatonin may be effective in migraine prevention in children (45).

Cyclic vomiting syndrome

Cyclic vomiting syndrome is a disorder that affects children. The mean age at onset is 5.2 years, but the syndrome can also occur in adults. According to the ICHD-3 criteria, the vomiting must be at least four times per hour. Children with this disorder are well between attacks. Attack frequency is about once a month, on average, and attack duration is typically several days. A personal or family history of migraine headache is common. The differential diagnosis for cyclic vomiting syndrome is broad: gastrointestinal pathology; urological disorders (46); neurological disorders, like autonomic seizures (Panayiotopoulos syndrome and Gastaut type epilepsy) (47); cannabinoid hyperemesis syndrome (48); and metabolic disorders (49). Case series have suggested that triptans are an effective acute therapy in some patients. Given the significant vomiting, typically nasal spray or subcutaneous sumatriptan are used; however, successful treatment with oral sumatriptan has also been reported. As the episodes are often quite debilitating, treatment with a migraine preventive may be worthwhile, although there are no randomized trials to guide agent selection. The North American Society for Pediatric Gastroenterology, Hepatology and Nutrition recommends amitriptyline for children aged ≥ 5 years and cyproheptadine for younger children. There is some evidence that amitriptyline may be superior to propranolol for cyclic vomiting syndrome prevention in children. The neurokinin-1 receptor antagonist aprepitant was found to be effective both as an acute therapy and as a preventive therapy (dosed twice weekly) in an open-label study (50).

Abdominal migraine

Abdominal migraine is likely the most common childhood periodic syndrome to present in a paediatric headache clinic, in one series accounting for 48.9% (51,52). The population prevalence has been estimated at 4.1% among 5–15-year-olds. Mean age of onset is 7 years. Usually, onset is in school-aged children and is characterized by bouts of abdominal pain lasting 2–72 hours. Typically, the pain is dull and often in the midline or poorly localized. The child may experience nausea, vomiting, anorexia, or pallor during the attacks. The children are well between attacks and no gastrointestinal pathology is identifiable. The mean attack frequency is 14 episodes per year, but with high variance. Mean attack duration is 17 hours, with a range of 1–72 hours (53). There are case reports of successful treatment of acute attacks with nasal spray sumatriptan. (54). As with cyclic vomiting syndrome, treatment with a migraine preventive may be worth consideration. A small case series suggests a course of intravenous dihydroergotamine (DHE) may be helpful for refractory abdominal migraine in children (55). If triptans are shown to be effective for acute treatment of abdominal migraine, it would be helpful to establish the PPV of successful termination of an attack with a triptan in a child presenting with recurrent migrainous abdominal pain. If the PPV is high, perhaps children could be spared invasive testing such as upper endoscopy and colonoscopy (56). In conclusion, there are as yet no randomized clinical trials to guide treatment for these disorders. In some cases, behavioural treatment, such as decreasing stimulation around a colicky infant, may be all that is needed and might be most appropriate in the youngest age group. In older children with frequent or disabling attacks, migraine preventives and acute treatments may be necessary and appropriate.

Benign paroxysmal torticollis of infant

Benign paroxysmal torticollis of infant is stereotyped paroxysms of torticollis during infancy (57). Its onset is usually in the first 6 months. Attacks last from hours to several days, and tend to occur with a certain periodicity. The disorder is self-limited and typically starts to improve by 2 years of age, resolving by the age f 3 or 4 years. There is evidence in some cases of an association with the genes associated with familial hemiplegic migraine (*CACNA1A, PRRT2*). There are no known effective treatments, although acutely antiemetics could be considered if there is significant vomiting. For prevention, cyproheptadine would be an option as it has been used in very young children (58).

Benign paroxysmal vertigo of childhood

Benign paroxysmal vertigo of childhood consists of recurrent attacks of vertigo, often with accompanying nystagmus and ataxia, with a normal EEG, and some assessment of audiometric and vestibular functions (59). Typical age of onset is between 2 and 5 years of age. The attacks are abrupt in onset and last just seconds to minutes. Although some children outgrow the disorder, for others' attacks persist into adolescence. In some cases, there is a genetic link between benign paroxysmal torticollis of infancy, benign paroxysmal vertigo of childhood, and familial hemiplegic migraine via mutations in the *CACNA1A* gene (58).

Comorbidities: physical and psychological

In children and adolescents, headache is one of the most common pain experiences and it is associated with a high risk of physical and psychiatric morbidities (see also Chapters 11 and 52) (60). Comorbidity can significantly influence medical care as it may confound diagnosis and offers special therapeutic challenges. Headache may persist into adulthood as a chronic condition.

Headache and migraine in children and adolescents are commonly associated with psychiatric and neurological comorbidity, in particular depression and anxiety, sleep disorders, attention-deficit hyperactivity disorder (ADHD), epilepsy. In addition to the overlap in clinical expression, migraine and epilepsy in the paediatric age group share common genetic underpinnings, a similar pathogenesis, and may be prevented using the same medications (61). An association with atopy and cardiovascular disease, especially ischaemic stroke and patent foramen ovale has also been shown (62–66). Also asthma, hay fever, and frequent ear infections were more common in children with headache, with at least one of these occurring in 41.6% of children with headache versus 25.0% of children free of headache. Other medical problems associated with childhood headaches include anaemia, overweight, abdominal illnesses, and early menarche (67).

Other conditions frequently observed in children with frequent or severe headaches are ADHD, especially hyperactive/impulsive behaviour and learning disabilities (68).

A higher comorbidity of headache, in particular migraine, with atopic disorders (asthma, rhinitis, or eczema), studied in a sample of children presenting with such disorders was also found. The prevalence of migraine was significantly higher in children with atopic disorders than in those without. The strongest association was detected with rhinitis (63).

Recent research suggests that obesity is significantly correlated with migraine frequency and disability in children, as in adults (69). Translational and basic science research has shown multiple areas of overlap between migraine pathophysiology and the central and peripheral pathways regulating feeding. Specifically, neurotransmitters such as serotonin, peptides such as orexin, and adipocytokines, such as adiponectin and leptin, have been suggested to have roles in both feeding and migraine. A relationship between migraine and body mass index (BMI) exists, and therefore interventions to modify BMI may provide a useful treatment model for investigating whether modest weight loss will reduce headache frequency and severity in obese migraineurs (70). Verrotti et al. (71) investigated the real impact of a weight loss treatment on headache in a sample of obese adolescents. In all, 135 migraineurs, aged 14–18 years, with a BMI ≥97th percentile, participating in a 12-month-long programme, were studied before and after treatment. The program included dietary education, specific physical training, and behavioural treatment.

Decreases in weight, BMI, waist circumference, headache frequency and intensity, use of acute medications, and disability were observed at the end of the first 6-month period and were maintained through the second 6 months. Both lower baseline BMI and excess change in BMI were significantly associated with better migraine outcomes 12 months after the intervention program. Attention to initial body weight and weight loss may therefore be clinically useful (71).

Migraine is probably the best-studied pain disorder in the context of comorbidity with anxiety and/or depression (72,73). Numerous population- and hospital-based studies have revealed a relationship between migraine or headache and psychopathology in children (74–77). Depression is more prevalent in headache patients than in the headache-free population (78). Pavone et al. (79) enrolled 280 children (175 boys and 105 girls), aged 4–14 years, affected by primary headaches and found a significant association of primary headache with anxiety and depression.

In a psychiatric setting, Masi et al. (80), in an exploratory study, examined the prevalence of somatic symptoms in a sample of 162 Italian children and adolescents with emotional and/or behavioural disorders. The sample was divided according to sex (96 boys, 66 girls), age (70 children < 12 years of age and 92 > 12 years of age), and psychiatric diagnosis (anxiety, depression, depression/anxiety, other). The authors observed that headache was the most frequent somatic symptom in children and adolescents referred for anxiety, depression, and behavioural disorders, with a higher prevalence in girls.

Cahill and Cannon (81) defined migraine as a subtype of headache of particular interest for psychiatrists, as they found a link between migraine, psychiatric disorders (mainly anxiety and depression), personality traits, and stress.

The nature of the relationship between migraine and anxiety is still not clear and we do not know if that relationship is specific to migraine or related to attack frequency (82), even if some data suggest the latter (83). It is well known that the risk of migraine is higher in patients with comorbid anxiety and/or depression (84), and that anxiety predicts the persistence of migraine and TTH (85). While only phobic disorder seems to be a predictor of the onset of migraine (86), anxiety, more than depression, predicts long-term migraine persistence, headache-related disability, and reduced perceptions of efficacy with acute treatment (85,87). Phobic disorder is also associated with more frequent and longer migraine attacks, particularly among males (88).

An increased risk of anxiety disorders in children and adolescents with migraine versus patients without migraine, is found in many studies. Arruda and Bigal (89), in their population-based study, confirmed the higher prevalence of anxious symptoms in children and adolescents with migraine.

In a meta-analysis of 10 studies published between 1996 and 2011 (406 patients, mean age 11.6 ± 2.3 years), Ballottin et al. (82) found that children with migraine show more psychological symptoms than healthy controls, detected by using the Child Behavior

Checklist. They emphasized the need for studies to compare children migraineurs with children affected by other chronic pain disorders in order to understand whether the psychopathological profile is related to migraine or to chronic pain.

Some studies suggest that psychiatric disorders might not be specifically related to migraine but to chronic illness in general: in a comparison of migraine with chronic non-headache pain, no difference was found in anxiety and depression levels between the two groups with chronic pain, with respect to pain-free controls (90). Another study compared headache patients and patients with recurrent abdominal pain and did not find psychological differences (internalizing vs externalizing disorders) (91). One of the hypotheses for the comorbidity is that common genetic and/or environmental risk factors may underlie both migraine and psychiatric disorders (86).

Gonda et al. (92) found that anxiety and migraine were associated with specific gene polymorphisms, supporting the hypothesis of a shared genetic linkage between these two conditions. There are also some studies that showed no correlation between migraine, anxiety, and depression. Parental ratings of anxiety, depression, shyness sensitivity, sleeping difficulties, perfectionism, psychosomatic problems (unrelated to headache), other behavioural disturbances, major life stress events, and parental expectations (i.e. achievement orientation) indicated that the headache children showed significantly higher shyness sensitivity, psychosomatic problems, and behavioural disturbances, and significantly lower parental expectations than the control group children, but no other differences were found (93). While none of the variables was predictive of the frequency or intensity of head pain, measures of anxiety, perfectionism, and life stress events contributed significantly to the prediction of the severity of head pain. Also, the study by Laurell et al. (94) showed conflicting data. The authors interviewed 130 schoolchildren and their parents, and found a predominance of comorbidity with other pains rather than psychological and social problems.

In addition to migraine, chronic daily headache (CDH), defined as ≥ 15 headaches per month, is associated with increased functional disability and impaired quality of life (95). Functional disability in children with recurrent headache has also been shown to be a risk factor for psychiatric conditions such as depression (96). While research in the area of adult headache has made great strides, little is known about the prevalence of psychiatric comorbidity in children with chronic headache conditions. Some researchers have suggested that children with headaches are at increased risk for psychological adjustment problems, including symptoms of anxiety and depression (97,98). A single study of a large sample of schoolchildren in Taiwan that did use standardized interviews indicated that nearly half (47%) of the sample of 122 children (out of > 7000 children) who reported chronic headaches had one or more psychiatric disorders, primarily mood or anxiety disorders (74). Two years later, the same authors identified a higher frequency of suicidal ideation in younger adolescents with migraine with aura or high headache frequency. These associations were independent of depressive symptoms (99). Antidepressant and antiepileptic use in adolescents was potentially associated with an increasing suicide risk and both frequently used in adolescents with migraine (100). Wang et al. (99) did not exclude the diagnosis of early onset juvenile bipolar disorders (JBD). Although the onset of JBD before the age of 10 years is rare and the first manifestation occurs most frequently between the age of 13 and 15 years, the diagnosis of JBD is more difficult in children and adolescent populations than in the adult population owing to the variation of symptoms. For example, in children and adolescents, dysphoria is more likely than a euphoric or depressive mood. Asymptomatic intervals rarely exist, yet rapid cycling prevails. In addition, it has been shown that antidepressants in JBD-affected children can have severe adverse effects, particularly the amplification of suicidal ideation. Parisi (100) stressed that the possibilities of manic switching and occurrence of suicidal ideation have to be closely monitored when clinicians prescribe antidepressants for the treatment of either migraine or depression in adolescents.

Slater et al. (95) assessed comorbid psychiatric diagnoses in young people with CDH and examined relationships between psychiatric status and CDH symptom severity, as well as headache-related disability. They showed that 29.6% of patients with CDH met the criteria for at least one current psychiatric diagnosis. Of these, anxiety disorders were the most common (16.6% of the sample). Mood disorders, however, were less prevalent (9.5%). The most common anxiety diagnoses were specific phobia (n = 14/169), generalized anxiety disorder (n = 10/169) and obsessive compulsive disorder (n = 8/169). Of the 16 participants with a depressive disorder diagnosis, eight had major depressive disorder, four had a diagnosis of dysthymia, and four met the criteria for other mood disorders.

Moreover, 34.9% met criteria for at least one lifetime psychiatric diagnosis. No significant relationship between psychiatric status and headache frequency, duration, or severity was found. However, children with at least one lifetime psychiatric diagnosis had greater functional disability and poorer quality of life than those without a psychiatric diagnosis. Furthermore, it is important to consider the impact of headache on family life and dynamics. Children with migraine seem to be characterized by a higher prevalence of familial headache recurrence and parents' psychiatric disorders than children with other headache subtypes (101). Only in the case of migraine does higher familial headache recurrence correlate with higher psychiatric comorbidity in children. The association between migraine and anxiety leads us to consider the need for an integrated medical and psychological approach to the taking care of these young patients and their families.

Impact: disability and quality of life

In 2010, the Global Burden of Disease reported migraine as one of the most disabling disorders.

Recurrent headaches can negatively impact a child's life in several ways, including school absences, decreased academic performance, social stigma, and impaired ability to establish and maintain peer relationships. In fact, the impact of headache on young people is substantial and includes lower ratings of quality of life, poorer physical and mental health, and more of days missed school (102). In one study, the authors report that at least 8 days are lost because of headache in a general recurrent headache population, and they report that the most bothersome features are the intensity and the duration of headache (103).

Children and adolescents suffering from headache rate their quality of life poorer, not only than healthy controls, but also compared with sufferers of asthma, diabetes, and cardiac diseases (104), and similar to that in children with arthritis or cancer (67). In

addition, headaches have been shown to be comorbid with a range of physical and mental health problems, including asthma, allergies (67), sleep disorders (105), suicidal ideation (99), emotional and behavioural problems (106), anxiety, and depression (85). However, most studies on disability and headache have been conducted in clinical populations, with a likely bias of self-selection of patients according to the severity of the clinical situation. Most studies on headache in children or adolescents did not take into account the presence of comorbid disorders in rating disability, and biases therefore occur.

Treatment

The treatment of headache in children and adolescents follows the same general principles and guidelines as for the treatment of adults. If a secondary headache is suspected, it is imperative to investigate and treat the underlying cause. Once it has been determined that headache is primary, a clear treatment plan should be developed that fully incorporates the needs and understanding of the patient and family. This treatment plan should address acute treatment with a goal of rapid, consistent response, without recurrence, and limitation of medication overuse, and preventive treatment when the headache frequency exceeds, on average, one per week or there is significant disability. The goal should be a frequency of 1–2 headaches per month and low disability. Biobehavioural treatment could be added to address healthy habits and coping with a pain disorder.

Acute treatment

The acute treatment of migraine should result in a consistent response with minimal side effects, a quick return to normal function, and limited dependence on rescue or secondary therapies. The mainstays of this treatment plan as in an outpatient setting are nonsteroidal anti-inflammatory drugs (NSAIDs) and triptans, while in the emergency department, infusion centres, and inpatient settings this would also include dopamine antagonists, valproic acid, and DHE.

In contrast to adults, there are several unique principles that apply to the acute treatment of headaches in children. As children are growing, medications may need to be adjusted for weight, while also taking into account the increased metabolic rate and pharmacokinetics of drug absorption and elimination. This is best accomplished with a weight-based dosing and, to a lesser extent, age-based dosing. A few studies have shown that the benefit of medications used in adults were also seen in children. This is possibly a result of applying adult study designs to children's studies, in combination with a higher placebo response rate in children. Additionally, there may be personal and social features that impact a child's ability to treat headaches (i.e. inability to swallow pills, need to treat in the school setting). When devising an acute treatment plan, all of these components must be considered.

A general treatment plan should include NSAIDs (especially ibuprofen), used early in the attacks at an adequate dose (7.5–10.0 mg/kg/dose). When this is incompletely effective, triptans should be considered, especially during more severe attacks. Two triptans are currently approved by the US Food and Drug Administration (FDA) for children—almotriptan for those aged 12–17 years and rizatriptan for those aged 6–17 years.

In a double-blind, placebo-controlled three-way crossover study that included children as young as 6 years of age (range 6–17 years), rizatriptan was found to be consistently more effective than placebo at 2 hours—74% for first treatment and 73% for second treatment versus 36% for placebo (107). This study used a 5-mg dose for children weighing 20–39 kg and a 10-mg dose for those weighing > 40 kg. Furthermore, rizatriptan was more effective at 1 hour (50% and 55%) compared with placebo (29%).

A randomized, double-blind, placebo-controlled trial of almotriptan in 866 adolescents (aged 12–17 years) found a 2-hour pain-relief rate that was significantly higher for all doses of almotriptan—6.25 mg (71.8%), 12.5 mg (72.9%), and 25 mg (66.7%)—compared with placebo (55.3%) (108). Further analysis demonstrated a superior sustained response with improvement in migraine-associated symptoms for almotriptan versus placebo, with the 12.5-mg dose associated with the most favourable response. However, analgesics are the most widely used for acute treatment for headache, although it has been known for the last 50–60 years that too frequent use of these medications can promote the progression of the headache, in terms of both pain intensity and duration (109).

Moreover, a significant problem is represented by the possibility of inducing a medication overuse headache (MOH). According to Olesen et al. (110), MOH can be described as head pain presenting 15 or more days per month, with an abuse of one or more symptomatic drug(s) for at least 3 months and a worsening of the headache during the same period. Epidemiological studies found that MOH has a prevalence in children and adolescents of between 0.3% and 0.5%, but a study found a prevalence of 9.3% in 118 patients (children and adolescents) seen at a third-level headache centre. The prevalence of MOH increased up to 20.8% in the subgroup of patients with CDH, granting the importance of a strong attention towards drug use in children and adolescents with headache, and especially with CDH (111,112). Medication overuse can be avoided by restricting the number of times acute medication may be used. General guidelines are to limit the use of non-specific analgesics to less than 2–3 times per week, while limiting migraine-specific agents to less than six times per month.

Preventive treatment

When headaches are frequent (more than once a week) or disabling (Pediatric Migraine Disability Assessment (PedMIDAS) score > 30—Grade III or W), preventative treatment can be considered. The goal of preventative treatment is to reduce the headache frequency (< 1–2 per month) and decrease disability (PedMIDAS < 10) for a sustained period of time (4–6 months). The presence of comorbid conditions may guide the treatment of choice. No medications are currently approved by the US FDA for the prevention of paediatric headaches, and the American Academy of Neurology only identified flunarizine (not available in the USA) as having sufficient evidence (113).

Agents that have been used for paediatric migraine prevention include antidepressant medications, including amitriptyline (114); antihypertensive medications, including propranolol (115–117); antihistamine/antiserotonergic medications, including cyproheptadine (118); and antiepileptic medications, including valproic acid (119–122) and topiramate (123–125).

Studies show greater rates of treatment discontinuation due to adverse effects with divalproex sodium 1000 mg daily, and an increased

risk of weight loss, paraesthesia, and respiratory tract infection with topiramate.

Parents are quite interested in the use of substances other than medications for treatment of childhood illness. Many vitamins, minerals, and supplements, like riboflavin, magnesium, and coenzyme Q10, have been touted as effective in reducing headache, but studies are more promising in adults than in children (126).

Both physicians and patients are often frustrated with the current therapeutic options in primary headache; however, there are several emerging therapies on the horizon (127). A therapy modality that has received significant attention is neurostimulation. Currently, transcutaneous neurostimulation remains in use but additional neurostimulation techniques and targets, including the vagal nerve, deep brain structures, occipital nerves, and sphenopalatine ganglion are being explored. Transcutaneous stimulation has been used with success in multiple primary headache disorders, although most studies currently are still in adults.

A few studies have looked at calcitonin gene-related peptide (CGRP) antagonists owing to the postulated role of calcitonin in headache pathogenesis. CGRP is postulated to be a target, particularly for migraine therapy. Botulinum toxin type A (BoNT-A) is relatively new to primary headache treatment. In one randomized, double-blinded, placebo-controlled trial of 571 patients with CDH, BoNT-A showed modest efficacy. BoNT-A treatment resulted in patients having, on average, approximately seven more (1 week) headache-free days versus baseline.

Biobehavioural therapy

Biobehavioural therapy, or the incorporation of adherence, education, lifestyle adjustment, and coping skills, is also essential to the management of paediatric migraine (127,128). Educating the patient and their family on the proper use of their acute and preventative medication, with a discussion about the importance of treatment and inclusion of the child in the decision-making process, may greatly improve adherence to the treatment approach. Healthy lifestyle habits are an important component of the treatment plan, to effect a lifelong response. Healthy habits include adequate hydration with limited use of caffeinated beverages; a healthy, balanced diet while avoiding skipping meals; regular exercise; and sufficient sleep on a regular basis. As discussed earlier, sleep disturbances have begun to be studied as a significant contributor to paediatric migraine, and treatment of the disturbances needs to be included in the treatment plan.

When the headaches are frequent, exceeding 15 days per month and/or disabling, additional biobehavioural treatment strategies may need to be employed. For adolescents with chronic migraine, the addition of cognitive behavioural therapy (CBT) to a multidisciplinary treatment plan, as discussed earlier, has been demonstrated to be highly successful. In a double-blind, attention-controlled study of CBT versus education control, CBT was demonstrated to have a superior response—both an absolute response and a 50% reduction in headache frequency—in adolescents with chronic migraine that was greater than the response seen for the pharmacological treatment of adult chronic migraine (129). Not only was this apparent during the treatment phase, but also the improvement was maintained for 12 months after the study treatment phase was completed. A promising adjunct treatment for adolescents with recurrent headaches is represented by mindfulness-based interventions (MBIs), a growing field of group-based, psychoeducational interventions that have been shown to reduce stress and alter the experience of pain, reduce pain burden, and improve quality of life. MBIs include mindfulness-based stress reduction and mindfulness-based cognitive therapy.

A pilot non-randomized clinical trial was conducted with 20 adolescent girls with recurrent headaches; no adverse events were reported. Parents reported improved quality of life and physical functioning for their child. Adolescent participants reported improved depression symptoms and improved ability to accept their pain rather than trying to control it. MBIs appear safe and feasible for adolescents with recurrent headaches. Although participants did not report a decreased frequency or severity of headache following treatment, the treatment had a beneficial effect on depression, quality of life, and acceptance of pain, and represents a promising adjunct treatment for adolescents with recurrent headaches (130).

We think that a multidisciplinary approach, which includes continuing counselling, education, and reassurance, in combination with pharmacological and non-pharmacological treatment, is an effective strategy for children and adolescents suffering from primary headaches.

Conclusion

The evaluation and management of childhood headaches is similar to adults when adjusted for development. The pathophysiology of primary headaches, especially migraine, has a clear genetic basis with environmental and developmental influences. These influences are likely the aetiology for the increasing prevalence of headache as children age and encounter more life-related comorbid conditions. Early recognition and management of headaches in children and adolescents should be expected to minimize the impact on these patients later in life. Long-term outcome studies on treatment and pathophysiological biomarkers are necessary to confirm these conclusions.

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51

Headaches in the elderly

Jonathan H. Smith, Andreas Straube, and Jerry W. Swanson

Introduction

Older adults are generally defined as individuals aged 65 years and older whose medical care may require unique diagnostic and therapeutic considerations. This age cut-off is arbitrary, and heavily influenced by societal norms, such as the age of retirement. Individuals aged 85 years and older ('the oldest old') represent the fastest-growing segment of the total population of most Western industrial countries. Therefore, appropriate medical care of this patient population has considerable socio-economic implications. Persistent, self-reported pain is common in the elderly, with a prevalence of 40–79% among the oldest old (1). Among older adults, sex differences are preserved in some conditions (i.e. back pain) but not others (i.e. visceral pain). Importantly, the comorbidity of depression with chronic pain also appears to remain stable across advancing age groups. Incident rates of chronic pain are thought to be similar between the < 50 and > 80 years age groups (~4.8 per 100 person-years) (2). Modifiable risk factors for incident chronic pain in the elderly include elevated body mass index, depression, and nicotine use, the latter only being significant in the setting of concurrent depression (2).

The epidemiology, assessment, clinical features, and treatment of headache as specifically pertains to the elderly will be discussed in this chapter. For detailed topical reviews, individual chapters should be referenced (i.e. Chapter 46, 'Giant cell arteritis and primary central nervous system vasculitis as causes of headache').

Epidemiology and clinical features of primary headache in the elderly

General

The prevalence of headache declines progressively following a peak prevalence at 45–50 years of age (3). Among older adults, headache continues to be listed among the most common sites of pain, along with lower back and limb pain (4–9). Furthermore, frequent headache continues to be common, with a reported prevalence of 11.3% in women and 0.5% in men, as noted in a population-based sample of individuals aged 60 years and older (10). In a study of elderly Chinese individuals, chronic daily headache (CDH) was noted in 3.9% (11). Notably, the age-specific prevalence rates were not statistically different between individuals 65–74 years and those aged 75–84 years (11). While headaches in the elderly are increasingly accounted for by tension-type headache (TTH), the overall burden of CDH remains unchanged (11,12). When followed longitudinally, a significant portion of elderly individuals initially diagnosed with chronic TTH may later receive a migraine diagnosis (13). Risk factors for CDH in the elderly include analgesic overuse, history of migraine, and depressive indices (11). However, these variables may not be associated with long-term prognosis, where up to 25% may continue to have CDH (13).

Migraine

In the American Migraine Study, men and women aged 60 years and older had a migraine prevalence of 2.5% and 7.5%, respectively (14). These estimates begin to gradually decline beginning around 40 years of age, when population peak prevalence occurs. Persistent migraine past the age of 60 years is not uncommon, an observation reproduced in other epidemiological studies worldwide (15–19). Incident migraine may continue to occur after the age of 50 years; however, it is unusual after the age of 60 years (20,21). New-onset headaches after the age of 50 years are always an indication for further evaluation of secondary causes (see 'Secondary causes of headache in the elderly'). The female predominance in migraine continues to be observed past the age of 70 years, but it does narrow marginally (14,15,22). Migraine with aura is rare in the elderly, although migraine aura without headache ('late-life migrainous accompaniments') is well described. Individuals aged 70 years and older have an odds ratio of 4.64 (95% confidence interval (CI) 3.1–6.8) of aura versus younger patients (23). Fisher highlighted the presence of positive features, and a characteristic temporal profile (5–60 minutes' duration, propagation of the phosphene from paracentral to the periphery and from posterior to anterior) in distinguishing these from cerebrovascular events (24).

While migraine is known to change in phenotype during the transition from adolescence to adulthood, further phenotypic transformations from adulthood to advanced ages are less well appreciated (25). In a large population-based study of age-dependent changes in migraine characteristics, the prevalence of migraine was 3.9% in those aged 70 years and older (23). The ratio of migraine to probable migraine was noted to be lowest at the extremes of age, decreasing steadily after the age of 50 years. Accordingly, the presence

of unilateral headache, throbbing pain, severe intensity, worsening with exertion, photophobia, and phonophobia decreased with age, while the prevalence of migraine aura increased (23). The presence of nausea remained prominent, even in individuals older than 70 years of age, while other studies suggest an age-related decline in the reporting of nausea (26). These observations are consistent with the observations of others, with some authors also noting an increased tendency for vegetative symptoms (i.e. pallor, dry mouth, and anorexia) with attacks (26,27). An appreciation of this evolving phenotype is critical for improved recognition of migraine in the elderly. The biological reason for that change is not understood.

Tension-type headache

TTHs are thought to be the most common primary headache disorder in the elderly, similar to younger adults (28). Among a general community aged 55–94 years, TTH had a 1-year prevalence of 35.8% (95% CI 32.7–39), with 18% being frequent and/or chronic (22). However, one should recall that migraine in the elderly may be easily confused for TTH, given the tendency for bilateral involvement and migrainous features to be less prevalent (23,27). Migraine should be considered a possibility in an elderly individual with a history of migraine, presenting with milder, indeterminate headaches. Along these lines many elderly individuals thought to have TTH may later receive a diagnosis of migraine when followed longitudinally (13). Furthermore, ominous secondary causes of headache may present with a tension-type phenomenology (see 'Secondary causes of headache in the elderly').

Trigeminal autonomic cephalalgias

Trigeminal autonomic cephalalgias (TAC) are generally regarded as disorders of the young, although incident cluster headache has been rarely reported past the age of 60 years (29). There is even one report of a 91-year-old woman with new-onset cluster headache (30). While only limited natural history data are available, cluster headache was noted to persist in 15.3% past the age of 60 years in one cohort study (29). The core clinical features are thought to persist in older adults, although the duration of the remission phase seems to increase over time (31). Likewise, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) and short-lasting unilateral neuralgiform headache attacks with autonomic features (SUNA) may have predominance for relatively older ages, and not uncommonly present after the age of 50 years (32,33). Finally, the TAC syndromes may all be mimicked by secondary aetiologies.

Hypnic ('alarm clock') headache

Hypnic headache is a rare primary headache disorder that has a strong tendency to occur in older adults (see also Chapter 26) (34). The true population prevalence is unknown, but is thought to be rare based on tertiary care experience (35,36). The headaches, by definition, arise nocturnally, are dull, and last for at least 15 minutes. Onset after the age of 50 years can be used as part of the International Headache Society diagnostic criteria. In a recent French series, 95% were 50 years of age and older at the time of diagnosis; however, many were in their forties at the time of symptom onset (36). Young-onset cases are also recognized in the literature (34). Finally, symptomatic (secondary) causes of hypnic headache may be seen, including stroke and mass lesions (34).

Cranial neuralgia

Advancing age is considered to be a major risk factor for two clinically important aetiologies of facial pain: trigeminal and postherpetic neuralgia (PHN; see also Chapter 27). Classical trigeminal neuralgia most commonly arises between the ages of 50 and 70 years. The characteristic syndrome consists of brief, intense lancinating pain, often triggered by touch, chewing, and/or talking. The maxillary (V2) and mandibular (V3) divisions are most commonly affected. The finding of sensory loss in the face should automatically prompt an evaluation for a secondary mechanism (37). In contrast, the pain of PHN may be more continuous, burning in quality, and associated with cutaneous allodynia. PHN most commonly involves the ophthalmic (V1) division. Advanced age is not only a risk factor for incident PHN following varicella infection, but also for more severe and persistent pain (38). Further risk factors are the number of skin lesions and female sex.

Secondary causes of headache in the elderly

In a community survey in Italy of incident headache in those aged 65 years and older, 15.3% had a secondary headache diagnosis (39). In a cohort review of 193 patients aged 65 years and older with new-onset headaches, 15% had a serious secondary cause versus 1.6% of younger patients (21). These included temporal arteritis, intracranial neoplasm, and stroke. Systematically asking elderly patients about red-flag headache features is therefore a critical part of the clinical evaluation (40). New-onset or changing headache pattern in an individual aged 50 years or older constitutes sufficient basis for a diagnostic evaluation, including neuroimaging and measurement of erythrocyte sedimentation rate (ESR) and C-reactive protein to screen for giant cell arteritis (GCA).

While headache is often a prominent presenting feature of GCA, clinicians should be aware that visual loss, double vision, jaw claudication, constitutional features, and symptoms of polymyalgia rheumatica may also be important clues to diagnosis (see also Chapter 46). Elevation of serum inflammatory markers is characteristic, but seldomly are low ESR measurements seen (41). Immediate initiation of treatment with corticosteroids and confirmatory testing with a temporal artery biopsy is considered the standard of care in order to prevent ocular morbidity (42).

Cerebrovascular disease is another important cause of headache in elderly patient populations. A history of a trauma within several months of an incident headache should prompt concern for subdural haematoma. Brain tumours often present with a tension-type phenomenology along with other neurological findings, with headache only rarely being an isolated symptom (43). Further, despite the common belief, early morning headaches are not a common feature (43). Elderly patients with cervical arthritis may report posterior headaches, although causality may be difficulty to confirm. Cervical arthritis is likely a common mechanism underlying occipital neuralgia in older patients, but imaging should be performed to exclude alternative structural lesions. Regardless, physical therapy interventions directed at cervical traction and stabilization may be of benefit.

Headache symptoms in the elderly may be related to systemic processes, comorbidities, and medication exposures. Sleep apnoea headache, for example, is typically a morning headache, which may remit within 30 minutes of waking (see also Chapter 57) (44). The headache most closely resembles a TTH (44). Haemodialysis sessions

may be complicated by a headache occurring within 72 hours of the session, which may be improved by modification of dialysis parameters (see also Chapter 40) (45). These headaches may be difficult to classify in patients with pre-existing headache diagnoses (45). Cardiac cephalalgia is another important consideration, which may be easily confused with episodic migraine, given shared symptoms of nausea, and exacerbation with activity (see also Chapter 28) (46). A point of differentiation is that cardiac cephalalgia will be improved by nitroglycerin, which exacerbates most idiopathic headache disorders. Finally, iatrogenic headache secondary to medications is not uncommon. A careful review of a patients medication profile is important in the evaluation, with the added benefit of potentially minimizing polypharmacy in an elderly individual.

Pain assessment in the elderly

The clinician should be aware of potential barriers to pain assessment in the older adult, which may accompany both normal ageing and acquired comorbidity, such as dementia and post-stroke aphasia (47). Older adults may erroneously view pain as a normal part of ageing, and may worry that reporting pain may lead to tedious testing, hospitalizations, and possibly loss of independence (48). Older patients need to be reassured of their autonomy, and counselled that pain in advanced age remains a treatable problem. In a large community-based study from Australia, differences emerged starting at the age of 60 years for older adults to be more cautious and reluctant to label sensations as painful (49). However, older adults were not more stoic or confident about their ability to tolerate pain (49).

Despite known age-related changes in peripheral, spinal, and supratentorial pain-processing centres (50), it remains controversial as to whether experimental pain thresholds change with normal ageing (51). Different experimental outcomes likely depend on the nature of the stimulus (electrical, thermal, ischaemic, etc.), intensity of the stimulus, site of application, and patient comorbidity (51). It should be noted that experimental pain is, of course, fundamentally different than clinical pain.

Self-report of pain, the gold standard of pain assessment, has been reproducibly demonstrated to decline with increasing levels of cognitive impairment (47,52,53). In one study of nursing home residents, increasing levels of cognitive impairment were associated with the inability to give an interpretable response to any of five self-report instruments for pain intensity (54). This may be at least one important reason accounting for presumed undertreatment of pain among individuals with cognitive impairment, when compared with cognitively intact patients in similar circumstances (i.e. postoperatively following a hip replacement) (53). Similarly, hospitalized stroke patients with aphasia are less likely to receive pain medications than those without aphasia (55). The topography of the specific dementia type may be important in determining the individual's response to pain (56). Along these lines, early studies suggested normal pain detection threshold but increased pain tolerance threshold in individuals with Alzheimer's dementia (57). The findings were hypothesized to be explained by the relative preservation of the primary somatosensory cortex, with degeneration of the limbic regions in the disease process (57). Surprisingly, subsequent functional neuroimaging studies have demonstrated not only preserved, but also enhanced, central processing of experimental pain in patients with Alzheimer's dementia (58). However, there is some experimental evidence that the placebo effect, which is an important part of medical treatment, is reduced or even missing in patients with Alzheimer's dementia (59).

In patients who are able to provide a self-report of pain, validity and reliability of standard self-report instruments are generally thought to be preserved in populations with cognitive impairment and post-stroke aphasia (47,60). Numerical rating and verbal descriptor scales are generally recommended, while the validity of the faces pain scale may become degraded in cognitive impairment (47). When assessing a patient with limited communication, one should appreciate that untrained observers tend to underestimate another individual's pain (61). Observational pain scales are being developed and validated; however, none is currently available for the assessment of headache specifically (47).

Treatment of headache in the elderly

Treatment of headache in the elderly has the potential to impact multiple important quality measures, including patient functional status, fall risk, socialization, and healthcare costs (62). Treatment of headache in the elderly, however, requires an appreciation of age-related changes in medication pharmacodynamics and kinetics, side effect tolerability, and treatment preferences (9,63–65). While elderly patients are at an increased risk of adverse drug events, pain can continue to be managed effectively with advancing age. The use of placebo is unethical and not appropriate in the management of geriatric pain (62). One should consider non-pharmacological approaches in this population, including regular aerobic training, physical therapy, acupuncture, and massage. Beside these interventions, psychological treatment as behavioural and relaxation therapy are further options. Unfortunately, many clinical trials have excluded individuals aged 65 years or older, limiting the availability of evidence-based treatment for this population. Headache management in the elderly therefore requires a careful extrapolation of experience from younger patient populations.

A working knowledge of age-related pharmacological changes is important. Gastrointestinal transit times slow, including delayed gastric emptying, which result in altered absorption rates. The ratio of fat to lean muscle mass increases with age, effectively increasing the volume of distribution for fat-soluble drugs. Both hepatic and kidney (decreased glomerular filtration rate (GFR)) function may change, resulting in altered metabolism and clearance of drugs. Finally, age-related chronic illness, such as chronic kidney disease, should factor into treatment considerations. Tricyclic antidepressants, and other anticholinergic drugs, may exacerbate an underlying neurodegenerative process, like Alzheimer's dementia. Interestingly, in a meta-analysis of treatments for PHN, the number needed to harm is actually greater for amitriptyline than for gabapentin, which is often thought of as a 'safer' medicine (66). Thus, caution is mandatory with all pain treatments in the elderly.

Acetaminophen may often be used as an effective abortive analgesic in the elderly, and may even be used up to 2 g daily in the setting of cirrhosis. Acetaminophen should be avoided, however, if there is ongoing alcohol use. Non-steroidal anti-inflammatory drugs should be used with caution, especially if there is concern

for gastric ulceration, reduced GFR, and increased blood pressure. Triptan and ergotamine analgesics should not be strictly prohibited in the elderly, but they do become relatively contraindicated if there is comorbid coronary, peripheral, and/or cerebrovascular disease. Of note, a large case–control study including patients aged 70 years and older did not find an association between triptan use and vascular end points (67). Promethazine may precipitate delirium in patients with dementia, and antiemetics and antidepressants should be used cautiously if there is QT interval prolongation on an electrocardiogram. Occipital nerve blocks are another alternative for abortive treatment when systemic pharmacotherapy becomes limited, but controlled studies are missing.

Preventative treatments in the elderly should universally be started at low doses, and only gradually increased, often to a lower target dose than that used in younger adults ('go slow and stay low') (63). Low-dose gabapentin in CDH is often a good first choice, especially if there is polypharmacy, hepatorenal impairment, and other sites of pain. In patients with dementia and behavioural dyscontrol, low-dose valproic acid can be helpful for both headache and impulse control. If avoidance of oral pharmacotherapy is desired, botulinum toxin treatment is an alternative for prophylaxis of chronic migraine.

Finally, just as in young adults, one should recall the importance of treating comorbidity that may interact with headache pathophysiology, such as sleep apnoea, temporomandibular and cervical osteoarthritis, and depression. Furthermore, other comorbidities, such as coronary artery disease and arrhythmia, may limit the use of certain medications.

Conclusions

Headache continues to be relatively prevalent among the elderly, a rapidly expanding subset of the population. Migraine may present as probable migraine in the elderly, and be easily confused for TTH. Secondary headache syndromes are common among older adults with incident headache, and should be systematically assessed for. Treatment of headache is limited by age-related changes in pharmacology and accrual of systemic comorbidity. However, this should not preclude appropriate abortive and preventative headache management.

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52

Headache and psychiatry

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Introduction

In 1895, Edward Liveing reported that patients with chronic headache are likely to experience depressive mood, irritability, anxiety, memory, and attention deficit. However, it was not until 1937 that Harold Wolff (1) first systematically studied these associations and defined the 'migraine personality' as a mix of 'personality features and reactions dominant in individuals with migraine', including 'feelings of insecurity with tension manifested as inflexibility, conscientiousness, meticulousness, perfectionism, and resentment' (2). Patients with chronic migraine (CM) frequently exhibit this personality, characterized by depressive and anxious symptoms (3).

Through examining clinical manifestations associated with frequent migraine, Sheftell and Atlas (4) posited that headaches are not just a symptom of depression, but headache and mood disorders share a number of pathophysiological bases. Patients suffering from various forms of headache often complain of numerous associated symptoms (e.g. behavioural and somatic), which may be explained by psychiatric comorbidity (5). Patients with CM headaches are more likely to experience somatic symptoms (6), especially for severe headaches with associated depression and/or anxiety. Moreover, CM is different from episodic type of migraine with aura (MA), migraine without aura (MO), and migraine aura without headache (without a history of characteristic migraine headaches). Endicott (7) found that the majority of patients with affective disorders had episodes with transient neurological symptoms similar to the aura symptoms that are observed in patients with migraine. The diagnosis of headache is often complicated by the emergence of new terms and criteria, whereas psychiatric disorder diagnoses are based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (8) multiaxial coding system. The prevalence and impact of psychiatric disorders associated with headache have been the focus of several studies investigating the association between migraine (and other types of headache) and major depression, illicit drug abuse, anxiety, nicotine dependence, and suicide attempts (9). Unfortunately, the relation between headache and psychopathology has often only been discussed clinically rather than studied systematically (10). However, this association is an important area for future headache research. Accordingly, the aim of the present chapter was to explore the prevalence and impact of mental illness among patients diagnosed with migraine headache (see also Chapter 11).

Historical context

Epidemiological research has demonstrated a strong association between primary headaches and psychiatric disorders (11–13).

Endicott (7) found that migraine headache was relatively common among patients with major affective disorders and occurred most frequently in patients diagnosed with bipolar disorder. Wang et al. (14) examined the comorbidity between headache and depression in an elderly sample, which had rarely been the focus of previous research. The researchers documented that patients with migraine were at a higher risk of depression than non-migraine patients.

More recently, several studies have found this relationship to be bidirectional (11). Specifically, individuals suffering from migraine headaches have more than a threefold risk of developing depression versus non-migraine patients, whereas depressed patients who have never previously suffered from migraine have more than a threefold risk of developing migraine versus non-depressed patients. The presence of migraine or severe non-migraine headache increases a patient's risk of experiencing depressive symptoms and/or panic attacks, whereas the presence of depression or panic disorder is associated with an increased risk of developing migraine, but not severe non-migraine headaches (15). Similarly, Hung et al. (16) found that mental stress and depressive symptoms were the most common precipitating factors for headache among patients with affective disorders. Further, they suggested that headache was not a symptom of depression, but shared pathophysiological bases contributed to headache and several mood and anxiety disorders.

Pathophysiological bases

Given the importance of genetic factors in both migraine headaches (17,18) and mood disorders (19–21), it is critical to examine the potential underlying mechanisms common to both conditions (15,17,22), with particular emphasis on neurochemical abnormalities (23). Recent studies of psychopathology and headache have shown neuropathic similarities between migraine and affective disorders (24), involving limbic activation (25). Neuroscience research and techniques such as positron emission tomography and functional magnetic resonance have found that pain and psychopathology (e.g. depression) are related to the same brain regions

(i.e. anterior cingulate, amygdala, orbito-frontal cortex and temporal lobe) (26). These findings suggest the sensitization of both the sensory and affective components of head pain as a possible phenomenon (27). Neuroplastic processes in corticolimbic structures, which are activated by both nociceptors and psychological stimuli over time, result in an integrated relationship between migraine (or pain) and psychiatric disorders in vulnerable individuals. This vulnerability may be attributed to a genetic variant of serotonergic dysfunction, alterations in monoamine systems, or channelopathy (i.e. a defect in calcium channels) (18). Consequently, the development of these two pathologies, starting from a familial risk related to serotonergic dysfunction, initially involving pain regulation and cerebral perfusion with primarily onset of migraine, may increase the risk for mood disorder onset (9,28–30).

Investigating the association between subtypes of migraine headaches and affective disorders should help identify a possible pathomechanism common to both disorders (31). Alterations in serotonergic systems are found in attempted suicide and suicide deaths (32), as well as in those involved in the pathophysiology of both migraine headaches (33) and affective disorders (34).

Epidemiology

Epidemiological and clinical research has consistently demonstrated an association between depressive, bipolar, and anxiety disorders with migraine headaches (35–37). Specifically, epidemiological data have demonstrated an association between migraine and mood disorders, with a lifetime prevalence of major depression being three times as high in patients with migraine versus patients without migraine (38). Among recurrent headache patients, affective disorders are diagnosed more than three times as frequently as in the general population, and the prevalence increases in clinical populations, particularly in those with chronic daily headache (CDH) (35,39). In another study, a comorbid psychiatric disorder was present in 90% of 88 clinical patients with CDH (40).

This comorbidity of CDH and psychiatric disorder seems to be more frequent in a particular type of patient. Taking into consideration different variables, it is possible to characterize an individual likely to experience a migraine headache.

Gender

Women are significantly more likely than men to have a migraine. Specifically, women are four times more likely to develop a migraine and twice as likely to develop major depression (35) and, compared to men, often receive a diagnoses of both migraine (24% vs 9%) and major depression (24% vs 13%) by the age of 30 years, with the relative female risk increasing for migraine in late adolescence and for major depression after about the age of 20 years. In an epidemiological study in Denmark, the sex distribution for both migraine aura without headache and MA was 1:2 (41).

However, another study reported that migraine aura without headache may be more common in men (42).

Age of onset

MA is associated with an early age of onset, and age explains the difference between the two migraine groups (MA and MO) better than the variables of suicide attempt (odds ratio 3.2, $P = 0.13$ (non-significant)) or affective temperament (31). Migraine onset occurred earlier than mood disorder onset, and Franchini et al. (28) did not find any difference in migraine distribution according to the polarity of mood disorder, consistent with a previous study (38).

Family factors

Mood disorder and migraine in first-degree relatives is significantly related to the risk for comorbidity (28).

Psychiatric disorders

Endicott (7) demonstrated that migraine was common in patients diagnosed with major affective disorders and occurred with highest frequency in those with bipolar disorder II (51% prevalence of migraine in patients with characteristics similar to patients with bipolar II).

Moreover, several studies confirmed the association of migraine with bipolar disorder (43,44).

Migraine subtype

Psychiatric comorbidity is more prevalent among patients with chronic forms of headache versus episodic forms, especially in patients with CM. Moreover, patients with chronic pain disorders, particularly fibromyalgia (45) experience increased levels of sleep disorders, bowel disturbances, and fatigue. For episodic headaches, comorbid psychiatric disorders are more prevalent in migraine than in tension-type headache (TTH) (45).

Migraine in children and adolescents

Headache is common in children and adolescents, with approximately 10–30% of children and adolescents reporting weekly or daily headaches (46). Migraine occurs in 3–15% of children (47,48), whereas, 9–33% of patients suffer from non-migraine headache at least monthly (49).

Risk factors

Many risk factors (e.g. genetic factors, depression, female sex) are independently associated with the development of psychiatric comorbidity in patients with migraines and CDH (50). Furthermore, previous researchers (e.g. (51)) have demonstrated a positive relationship between the frequency of headaches and the level of depression in headache patients, with mood disorders being more frequent in patients who had chronic headache for 5 years or more. A report of two cases showed that decreased depressive symptoms were associated with a reduction in headache severity (52).

Both CM and chronic TTH (CTTH) share a similar personality profile in women, suggesting the involvement of these factors in the chronicity of headaches (53,54). An association between headache and certain personality traits or psychiatric disorders has also been reported in adults (17,55). In children, specific traits, such as rigidity and emotional inhibition, have been found in children with primary headache (56,57). Children with TTH were also more likely than migraine patients to possess the temperament traits of shyness and irritability (58)

Lafittau et al. (59) reported that transformed migraine is associated with an increased disability concerning housework, leisure, job, and social activities. Statistical analysis found higher emotional

distress scores (Hospital and Anxiety Depression scale mean score 32.2 ± 10.9) in patients with transformed migraine than in patients with sleep migraine (24.1 ± 7.3) ($P < 0.001$). Patients with transformed migraine were characterized by different coping strategies against pain (e.g. 'dramatization', 'distraction' and 'pray'), which are considered as dysfunctional coping strategies, although patients with sleep migraine used 'reinterpretation', which is associated with improved adjustment related to disability and emotional distress (60).

Migraine and psychiatric disorders

Migraine and Hamilton Rating Scale scores

The Hamilton Depression Rating Scale (HAM-D), one of the most used clinical scales for measuring depression, assesses headache on two items, whereas the Hamilton Anxiety Rating Scale (HAM-A) includes one item assessing headache. The average scores on the HAM-A and HAM-D were higher in headache sufferers than in healthy people. Moreover, the frequency of headaches, the history of headaches, and sex (women more than men) were correlated with scores on both the HAM-A and HAM-D (61).

Psychiatric disorders and headache

Psychiatric comorbidity was found more frequently in patients with chronic pain syndromes (62), and recent research shows a strong association between psychiatric disorders and headache, both CDH and TTH. This relation is complex and multifaceted, with existing studies confirming high rates of comorbidity between psychiatric disorders (especially depression and anxiety) and migraine and TTH. This finding implicates comorbid psychiatric disorders as a risk factor for headache progression and chronicity, while highlighting the need for assessment and treatment of relevant disorders (63).

In a prospective study, Merikangas et al. (17) found support for the hypothesis that anxiety contributes to the onset of a primary headache, acting as trigger for the development of mood disorders such as depression. They suggest that migraine occurs several years after anxiety, whereas it precedes the onset of depression by approximately 4 years (17).

In a community-based study, a high comorbidity with psychiatric disorders and suicide risk was found in adolescents with CDH. The presence of migraine, particularly MA, substantially contributed to these associations (64). Patients with migraine, anxiety, and chronic depression also had poor health-related quality of life (16,65). These comorbidities have been identified in several epidemiological (9,35,36,39) and clinical (39) studies of patients seeking treatment. Depression, bipolar, and anxiety disorders have been found to be the most common psychiatric conditions related to migraine (17,66). In both children (67) and adults (17,68), these psychiatric comorbidities are more specifically related to migraine than to TTH.

In patients with episodic migraine, the presence of anxiety and/or depression is characterized by elevated muscle tenderness in the head and/or neck, which often facilitates the development of chronic headache (53). In individuals with an episodic migraine without other psychiatric comorbidities, headache may be considered to be a manifestation of a somatoform disorder (e.g. conversion disorder, hypochondriasis) (8), similar to other somatic complaints such as fatigue and gastrointestinal symptoms.

It is important to distinguish between MA or MO and migraine aura without headache. As demonstrated in one population-based epidemiological study (17), MA was associated with multiple anxiety disorders, recurrent brief depression, and hypomania, whereas only the phobic and panic disorders were more frequent in patients suffering from MO. Moreover, no difference was found between patients with TTH and controls with respect to any of the affective or anxiety disorders. Oedegaard et al. (31) found that many patients presenting with major affective disorders experienced a migraine aura without headache. Of these patients, they reported a low level of the affective temperament and a low probability of having made a suicide attempt, as well as were older at the onset of migraine auras, versus patients suffering from MA (31).

Verri et al. (40) found an association between CDH and at least one psychiatric disorder in 90% of their cases, mainly generalized anxiety disorders (69.3%), followed by major depression (25%) and dysthymia (17%). Verri et al. (40) and Juang et al. (69) affirmed that a long-standing major depressive disorder and chronic depression were the most commonly found comorbidities in these patients (40), especially when the chronic headache syndrome had lasted for > 5 years. However, Juang et al. (69) found that the frequency of any anxiety disorder was significantly higher in patients with CM compared with those with CTTH.

In previous studies, the comorbidity between TTH and psychiatric disorders has been investigated only in clinical populations in which it has been shown that this association was more frequent in CTTH than in episodic TTH (11), and that anxiety and mood disorders were higher in the patients with CTTH than in controls (70), with significantly higher anxiety and depression scores in CTTH compared with headache-free patients (71,72). Moreover, among patients with episodic TTH, especially in CTTH, affective disorders have been found to be more frequent (73). No significant differences found between migraine and TTH with regard to psychiatric comorbidity (72,74,75).

As compared to affective disorders, personality disorders have been less frequently examined in empirical headache research. Patients with TTH had significantly higher scores on measures of automatic thoughts and alexithymia, and lower scores on assertiveness than healthy controls (76). Patients with CTTH had more automatic thoughts than patients with episodic TTH. In another study with a small sample of patients with CDH, using the Minnesota Multiphasic Personality Inventory, II version (MMPI-2), scores above the clinical cut-off were reported on the hysteria, hypochondriasis, psychasthaenia, depression, and social introversion scales (77).

As compared to patients with migraine, patients with TTH reported higher scores for the temperaments of emotionality and shyness, and lower scores for sociability (58). High scores on emotionality and shyness can be considered to be symptoms of 'behavioural inhibition' (78,79), which seems to increase the vulnerability for depressive and multiple anxiety disorders in children (80,81). Patients with TTH may have, as a group, more behavioural, emotional, and temperament difficulties than children referred for migraine (58).

This conclusion seems to be at odds with an epidemiological study in Finland, which found that psychiatric symptoms tended to be more strongly associated with migraine than with TTH, with the exception of similar anxiety symptoms being found between

Table 52.1 Prevalence of migraine in bipolar disorder from representative studies.

Source	Method	Sample size	Migraine prevalence (%)
Blehar et al. (115)	Medical section of Diagnostic Interview for Genetic Studies (DIGS)	n = 327 (186 F)	Total 21.1 (female 26.5)
Cassidy and Flanagan (116)	Self-report of headache	n = 100	Total 49.0
Mahmood et al. (43)	Self-report of IHS migraine criteria	n = 81 (37 F)	Total 25.9 (female 27.0)
Marchesi et al. (117)	Diagnosis by neurologist	n = 30	Total 20.0
Fasmer and Oedegaard (38)	Administered IHS migraine criteria	n = 27	Bipolar I 13.0 Bipolar II 77.0
Younes et al. (118)	Mother's report of past diagnosis of migraine	n = 21	Total 28.6 (female 0, male 21)

IHS, International Headache Society.

Adapted with permission from Springer Nature, *Journal of Headache Pain*, 10, Pompili M, Di Cosimo D, Innamorati M et al. Psychiatric comorbidity in patients with chronic daily headache and migraine: a selective overview including personality traits and suicide risk, pp. 283–290. © 2009.

groups (82). However, personality disorders are considered to be a complication for headache management (83–85), and significant headaches are often a complaint in approximately 60% of patients with personality disorders presenting for acute treatment at hospital emergency departments (86).

Tables 52.1 and 52.2 provide details about representative studies regarding the prevalence of migraine in bipolar disorder, as well as studies presenting the association between migraine and depression.

Suicide risk

We have already described the shared pathophysiology between migraine, depression, and suicide (9,29,30). Suicide attempts seem to be more frequent in patients suffering from migraine than in the general population, especially in females and in patients with MA (87). These risk factors for suicidal behaviour were also found in the general population (9,17,68,83). In contrast, CDH subtypes, headache frequency, or medication overuse were not found to be correlated with suicidal behaviour (64). Suicide attempts (15) have been shown to be associated with migraine, and MA also independently predicted elevated suicidal risk (score > 10 on the Mini International Neuropsychiatric Interview (MINI) Suicidality Module) in adolescents with CDH (64).

Wang et al. (88) investigated the association between migraine and suicidal ideation in a non-referred sample of 3963 adolescents. Compared to young people without migraine, those with migraine reported a higher frequency of suicidal ideation (16.1% vs 6.2%), especially those with MA (23.9%). Moreover, suicidal ideation was associated with higher headache frequency and headache-related disability; however, after controlling for depression scores and sociodemographic characteristics, the association remained significant only for MA and high headache frequency. In sum, the relation between MA and depression appears to be bidirectional (15).

Hesdorffer et al. (89) demonstrated that the co-occurrence of major depression, suicide attempts, and MA increased the risk of

Table 52.2 Selected studies presenting the association between migraine and depression

Study	Method	Migraine and depression, OR (95% CI)	Bi-directional relationship, OR (95% CI)
Longitudinal studies			
Breslau et al. (35)	IHS migraine criteria	Not assessed	New-onset migraine 3.5 (2.2–5.6) New-onset depression 3.6 (2.6–5.2)
Breslau et al. (15)	IHS migraine criteria	3.5 (2.6–4.6)	New-onset migraine 2.8 (2.2–3.5) New-onset depression 2.4 (1.8–3.0)
Breslau et al. (119)	IHS migraine criteria	Not assessed	New-onset migraine 3.4 (1.4–8.7) New-onset depression 5.8 (2.7–12.3)
Cross-sectional studies			
Merikangas et al. (67)	Diagnosis by neurologist	2.2 (1.1–4.8)	Not assessed
Breslau et al. (15)	IHS migraine criteria	3.5 (2.6–4.6)	New-onset migraine 2.8 (2.2–3.5) New-onset depression 2.4 (1.8–3.0)
Swartz et al. (100)	IHS migraine criteria	3.1 (2.0–4.4)	New-onset migraine 0.68 (0.02–2.0)
Zwart et al. (120)	IHS migraine criteria	2.7 (2.3–3.2)	Not assessed
McWilliams et al. (121)	Diagnosis by neurologist	2.8 (2.2–3.7)	Not assessed
Patel et al. (122)	IHS migraine criteria	Strict migraine 2.7 (2.2–3.3) Probable migraine 1.9 (1.5–2.4)	Not assessed

OR, odds ratio; CI, confidence interval; IHS, International Headache Society.

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unprovoked epileptic seizures more than the risk associated with either major depression or MA alone. The authors suggested that combinations of major depression, suicidality, MA, and epileptic seizures may constitute a cluster of conditions not hitherto described. Thus, it is possible that the association among these conditions reflects a causal pathway where one brain dysfunction (e.g. manifested by major depression) affects other brain dysfunctions (e.g. manifested by MA and unprovoked seizures) (89).

A history of MA, but not MO, is associated with increased suicide ideation and attempts in patients with major depression (9,36,64) and with current or previous affective episodes (31,38). Oedegaard et al. (31) found that 17% of patients having migraine aura without headache had made a suicide attempt and had a lower frequency of the affective temperament, as well as an higher age of onset of migraine auras, compared with patients with MA. However, the frequencies of suicidal thoughts were approximately equal in both groups.

In adult outpatients with a diagnosis of CDH (n = 116), de Filippis et al. (90) found that 28% had moderate-to-severe depression and 35% had severe hopelessness. The results also indicated that quality of life, temperament, illness perception, and psychological turmoil were associated. However, only the MINI suicidal intent score was associated with the quality of life when all variables were included in the analyses. Thus, suicide risk may play a central role in affecting the quality of life of patients with chronic headache (90).

The pain associated with headache is itself a potential independent risk factor for suicide, particularly in those with chronic headache or multiple sources of co-occurring pain (91). Individuals suffering from chronic pain may be particularly appropriate for suicide screening and intervention efforts. Innamorati et al. (92) proposed a new scale, the Italian Perceived Disability Scale, as a screening tool to identify comorbidity with emotional distress and disorders. This scale has proven to successfully predict suicidal intent in patients with CDH and to assess disability in patients with CDH (92).

Substance dependence and abuse

The impact of headache on the individual and society is a public health issue. About 4–5% of the general population suffers from frequent, almost daily headache, (93). In large population studies, researchers have indicated that patients who have low-frequency episodic migraine or high-frequency episodic migraine will transition to CM at a rate of about 2.5% per year (94). Evers et al. (95) have reported that medication overuse headache (MOH) was present in 8% of headache patients referred to a neurological clinic, whereas Aaseth et al. (96) reported that the prevalence of MOH was 3.7% in the general population.

Psychiatric comorbidity is common in patients with MOH (97) and seems to play a role in the development of migraine to MOH, and may also be linked to medication overuse in migraine patients (98). Pakalnis et al. (97) found that headache patients had significantly more symptoms of anxiety, depression, and somatization compared with controls. Patients with CDH were at a higher risk for emotional disorders, and medication overuse was a significant occurrence in this group. Moreover, Mitsikostas and Thomas (72) replicated this finding in patients with MOH.

Migraine is associated with substance abuse, nicotine dependence, and illicit drug use (99); however, substance use disorders have only been examined in three cross-sectional studies. Breslau et al. (9) found an increased risk of alcohol and drug abuse in migraine sufferers, whereas Merikangas et al. (17) and the Epidemiological Catchment Area Study (100) did not. These discrepant findings may be explained by the high comorbidity of substance abuse and bipolar disorder in the study by Breslau et al. (9).

Comorbid psychiatric disorders may increase the need for analgesics to be prescribed in headache patients (101,102), which may alter the functioning of the central serotonin system and heighten the risk for depression (103). Depressive patients may have decreased pain thresholds, resulting in analgesic overuse for the relief of their headache.

Prognosis

Psychiatric comorbidity complicates the management of patients with headache, and the prognosis for headache treatment is poor (11,104–107). In an 8-year follow-up study of 100 young adults with headache, researchers (24) examined the relations between psychiatric disorders at initial evaluation and headache status at follow-up. Patients with two or more psychiatric disorders at initial evaluation did not improve or deteriorated with regard to headache in 57% of the cases at follow-up. Moreover, only 29% cases were improved, while only 14% cases were headache free (24). In contrast, patients with no or only one psychiatric disorder exhibited greater headache improvement 8 years after the initial evaluation. Furthermore, only 15% cases were the same or worse, whereas 53% cases were improved and 40% cases were headache free (24). Migraine and depression independently decrease patient's quality of life (108).

The results of studies on the predictors of the outcome of CDH are variable. Some authors have reported that the predictors of persistent headaches include the presence of major depression (64), whereas others have reported that depression did not predict the persistence of CDH (14). Depression is associated with increased personal suffering, mortality (suicide is the most common causes of death in patients with major depression), utilization of healthcare services, and decreased functioning and quality of life (109–111). Other researchers have reported that the levels of emotional functioning (70) and the perception of stress, independent of the level of pain at baseline (112), predicted the frequency, intensity, and duration of headaches. Among depressed patients, given the stressful nature of headaches, headache attacks are triggered and/or exacerbated by stress and depressed mood.

Conclusions

Migraine is a leading cause of disability worldwide (113). Our analysis of the literature indicated a strong association between primary headaches and psychiatric disorders (11). The evidence of a link between chronic headache and mental health is not a recent finding. As previously mentioned, in 1895, Liveing described the occurrence of depressed mood, irritability, and anxiety in patients with chronic headache (114). However, recently, more rigorous and sophisticated research has indicated that this association may be explained

by shared neuropathic mechanisms between pain and affective disorders (24,25).

Moreover, research has demonstrated an association among suicide attempts and migraine (15), and also indicated that MA may predict an elevated suicide risk in adolescent patients with CDH (64). Recent studies are consistent with these results, and indicate that patients with diagnosis of CDH and migraine experience severe hopelessness (90) and perceived disability (92). These findings suggest that psychological assessment is necessary in patients with CM, and, conversely, that the presence of CM or headache have to be carefully monitored in patients with mental illness.

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53

Headache and hormones, including pregnancy and breastfeeding

Sieneke Labruijere, Khatera Ibrahimi, Emile G.M. Couturier, and Antoinette Maassen van den Brink

Characteristics and prevalence

Migraine is much more common in women than in men, which is largely attributable to the changes in ovarian female sex hormones throughout the reproductive life cycle of a woman (1,2). At a very young age, there is a slightly higher migraine prevalence in boys, but this difference disappears and switches to an increased prevalence in girls in the years around puberty (3,4). Remarkably, a recent study showed that non-obese men with migraine exhibited increased levels of the sex hormone oestradiol and showed clinical evidence of relative androgen deficiency (5). Even before menarche, a cycling pattern of female hormones is seen in girls, as well as a monthly pattern of migraine attacks (6). It must be stressed that hormonal fluctuations are not the cause of headache, but act as triggering factor superimposed on a genetic vulnerability to migraine

After puberty

Migraine prevalence is highest during the fertile part of a woman's life, when approximately 25% of all women experience migraine attacks versus about 8% of all men (**Figure 53.1**) (7,8). Within women, differences exist in the type and frequency of migraine attacks. It is common for attacks to occur around the time of the menstrual cycle and these menstrually related attacks are generally without aura (9). Hormone-related migraine in women is divided into four types, according to the International Classification of Headache Disorders, third edition (ICHD-3) (**Table 53.1**) (10). The most common form, present in approximately 35–50% of female migraineurs, is menstrually related migraine (MRM). About 80% of women suffering from this form of migraine also have attacks not related to their menstruation (11–13). A small proportion (about 20%) of women with MRM have migraine attacks exclusively during menstruation and this form is called pure menstrual migraine (9). The female hormone 17β-oestradiol is thought to play an important role in the increase in migraine attacks during menstruation. Progesterone is suggested to be involved in menstrual migraine as well (14,15). Possible underlying mechanisms are discussed further on in this chapter. **Figure 53.2** shows the relationship between female hormone levels and migraine attacks. Migraine attacks are especially likely to occur when oestradiol levels drop just before menstruation, after childbirth, or during the perimenopausal phase (14).

Exogenously administrated hormones can also influence migraine attacks. The effect of combined oral contraceptives and hormonal intrauterine devices on headache attacks has been extensively studied (16). Approximately 20–30% of women who use exogenous hormones on a regular basis for contraception, or hormone replacement therapy, experience new onset or worsening of migraine. This form of headache is called exogenous hormone-induced headache (10). These attacks often disappear with discontinuation or after prolonged use (16–18). Improvement of migraine symptoms, especially aura, may also be observed after use of hormonal contraceptives, but only in a minority of women. Progestins might be important in this improvement, but more studies are needed to confirm this observation (16,19). Additionally, discontinuation of hormones can also lead to headache or migraine attacks and is called oestrogen-withdrawal headache. This form of headache is most common during the pill-free interval of oral contraception use (20). It is reported in up to 70% of women using oral contraception (21).

Pregnancy

During pregnancy oestradiol levels are 10–100 times higher than in normal cycling women. About 50–90% of women suffering from migraine without aura (MO) report improvement of their migraine attacks, especially during the second and third trimester of their pregnancy. In 10–20%, attacks may even disappear completely during pregnancy. Oestrogen levels increase during each trimester and negatively correlate with migraine incidence. It is suggested that the absence of fluctuations in oestradiol levels are responsible for the decrease in migraine frequency during pregnancy (22–25). Migraine attacks with aura (MA) can also improve during pregnancy, but more often remain the same or worsen compared to MO attacks (26,27). When migraine attacks start for the first time during pregnancy, which occurs in 2–15% of pregnant women, these attacks are more often attacks of MA than MO (26–28). Often, no change in frequency of attacks is observed in women who already

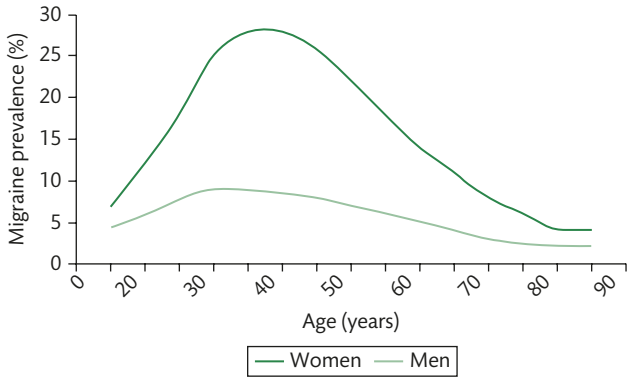

Figure 53.1 Global age-standardized point prevalence of migraine in men and women.

Prevalence expressed as a percentage of the population.

Adapted from *The Lancet Neurology*, 16, 1, Vetvik KG and MacGregor EA, Sex differences in the epidemiology, clinical features, and pathophysiology of migraine, pp. 76–87. Copyright (2016) with permission from Elsevier.

suffered from MA before pregnancy (26). After pregnancy, migraine returns back to the pattern observed before pregnancy in most cases. Approximately 30–40% of all women suffer from headache during the first week postpartum. This is most prevalent in women who were already migraine sufferers (28). The drop in oestrogen levels after delivery is thought to play an important role in the development of these attacks (29).

Lactation

Lactation can inhibit ovulation and may therefore influence female sex hormone levels (30). A few studies have investigated migraine prevalence during exclusive breastfeeding, and the results are contradictory. A large prospective study in Norway in women with migraine did not show any influence of breastfeeding on migraine (31), and a study in the USA in women with both tension-type headache and migraine revealed no effect of breastfeeding on headache prevalence (32). However, studies in Japan, Brazil, and Italy showed decreased recurrence of migraine in the first months after pregnancy during breastfeeding (22,28,33). The effect of partial breastfeeding on migraine prevalence has not yet been studied. Overall, although prevalence studies are contradictory, anovulation caused by breastfeeding is thought to lead to a decrease in menstrual migraine in breastfeeding women (28).

Menopause

The menopause is defined as the day of the last menstruation of a woman, which is determined 1 year after this event. During the transition phase from normal ovulation towards the menopause, worsening of migraine symptoms is often observed, undoubtedly due to changing hormone levels (Figure 53.2). These effects are seen on migraine attacks without aura, which are often related to the menstrual cycle, but not on migraine attacks with aura (34,35). After menopause, the frequency of migraine attacks without aura often decreases, the attacks become less severe or even disappear (36–38). In a study on spontaneous postmenopausal women, a migraine prevalence of 10.5% was observed (37,39), which is considerably less than the 25% prevalence that is seen in normally ovulating women. After menopause, oestradiol levels become stable and this is thought to be responsible for the decrease in migraine seen in postmenopausal women. There is also a differential effect on migraine based on the type of menopause. After a surgical menopause, there is less relief of migraine symptoms than after a natural menopause; hence, it has been suggested that older ovaries may produce factors that improve migraine symptoms (40).

Pathophysiology

During the menstrual cycle, female hormone levels fluctuate (Figure 53.2). Oestradiol levels drop abruptly just before menstruation. This drop in plasma oestradiol level is thought to play an important role in the generation of migraine attacks that are often seen at this point of the cycle. Indeed, administration of oestradiol during this period can postpone a migraine attack (14,41). A sustained high level of oestradiol is likely required before this precipitous drop in oestradiol level in order to trigger a migraine attack. This could explain why the increase in migraine incidence around ovulation is only modest (41).

Table 53.1 Characteristics and prevalence of four subtypes of hormone-related migraine in women.

	Characteristics according to ICHD-3 (10)	Prevalence
Pure menstrual migraine without aura	• Migraine attacks fulfilling ICHD-3 criteria 1.1 • Exclusively during menstruation • In at least two out of three menstruations	7% of migrainous women (~1.8% of all women) (9)
Menstrually related migraine without aura	• Migraine attacks fulfilling ICHD-3 criteria 1.1 • In at least two out of three menstruations • Additional attacks at other times during the cycle	22% of migrainous women (~9% of all women) (9)
Headache attributed to exogenous hormones	• Headache or migraine according to ICHD-3 criteria • Headache develops or worsens significantly after hormone intake • Headache improves or resolves after reduction or ending of hormone intake	Worsening of headaches in 30% of oral contraceptive users, new onset headache in 5–13% of oral contraceptive users (18)
Oestrogen withdrawal headache	• Headache or migraine according to ICHD-3 criteria • Headache or migraine develops within 5 days after interruption of daily consumption of exogenous oestrogen for 3 weeks or longer (often during the pill-free interval of oral contraception or following hormone replacement therapy)	70% of oral contraceptive users (16)

Source data from *Cephalalgia*, 38, 1, The International Classification of Headache Disorders, 3rd edition, pp. 1–211. © International Headache Society 2018.

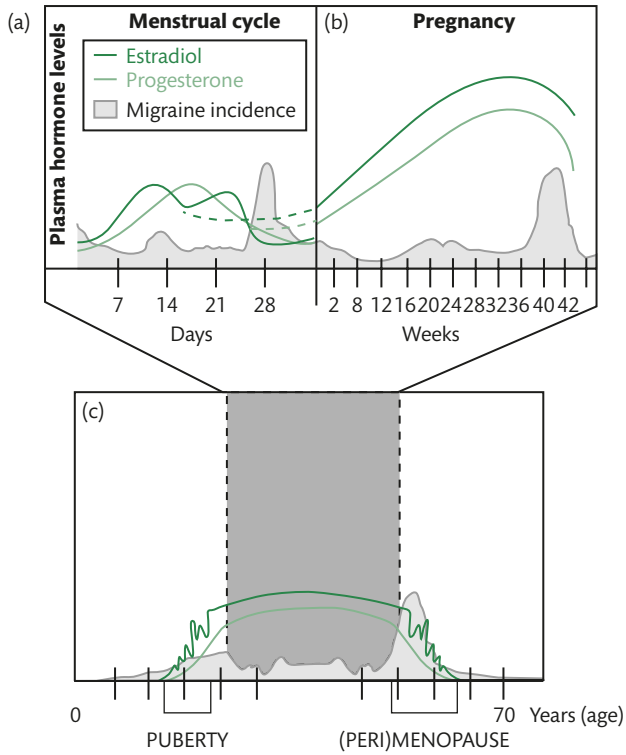

Figure 53.2 Migraine incidence and female hormones during the menstrual cycle, pregnancy and a woman's life.

Adapted by permission from Springer Nature, *Journal of Headache and Pain*, 13, 3, Sacco S, Ricci S, Degan D, et al, Migraine in women: the role of hormones and their impact on vascular diseases, pp. 177–189, © 2012.

17β-oestradiol

17β-oestradiol is a small lipophilic molecule that is mainly produced by the ovaries and is capable of crossing the blood–brain barrier (BBB). There are two different types of pathways via which oestradiol can exert its effects: genomic and non-genomic pathways. Genomic pathways can be activated via binding to the intracellular oestrogen receptors: oestrogen receptor alpha (ERα) or oestrogen receptor beta (ERβ) (42). After binding to ERα or ERβ in the cytoplasm, the complex enters the nucleus and oestradiol can bind to oestrogen-responsive elements on the DNA, thereby influencing gene expression (43). Furthermore, oestradiol can activate genomic mechanisms via binding to the membrane-bound G protein-coupled oestrogen receptor, activating intracellular signalling pathways that influence gene expression, like the mitogen-activated protein kinase/extracellular regulated kinase pathway (44). Oestradiol can also influence gene expression via epigenetic mechanisms, for example by changing the amount of promoter methylation of a target gene (45). The fast non-genomic pathways can be activated through binding of oestradiol to membrane-bound oestrogen receptors, activating different intracellular signal transducing pathways, leading, for example, to vasodilatation (46) and inhibition of apoptosis (47).

In a recent study on women with migraine, migraineurs were characterized by a faster late luteal phase decline in conjugated urinary oestrogens than in those without migraine (48). Furthermore, oestradiol levels in patients with MRM were recently reported to be higher at day 19–20 of the cycle in healthy controls versus MRM patients (49).

Effects of oestradiol on neurotransmission

Oestradiol can easily cross the BBB, where it can exert its effects, but it is also thought to be locally synthesized in the brain (50,51). Important brain structures that are involved in migraine pathophysiology, especially via transmission of nociceptive information, are the trigeminal system, cortex, brainstem, and thalamus, which can all be affected by oestradiol.

Cortical excitability changes during the menstrual cycle (52), and high oestradiol levels can increase neuronal excitability and sensitivity of the brainstem and trigeminal nucleus caudalis via non-genomic pathways (43). Oestradiol has been shown to influence gene expression in the trigeminal ganglion of the rat (53), a structure that is involved in migraine attacks, and a decrease in oestradiol levels has shown to inhibit neuropeptide Y gene expression, which is an inhibitor of synaptic calcitonin gene-related peptide (CGRP) release (54).

Oestradiol can affect different neurotransmitter systems, including the serotonergic, glutamatergic, γ-aminobutyric acid (GABA)-ergic, and CGRP-ergic system, which are all neurotransmitter systems involved in pain signalling in migraine pathophysiology. Serotonin synthesis and neuronal firing are influenced by oestradiol levels. Monkeys treated with oestradiol showed a ninefold increase in tryptophan hydroxylase mRNA expression, a rate-limiting enzyme for serotonin synthesis, versus controls (55,56). Furthermore, oestradiol can enhance the glutamatergic system by causing increased dendritic spine formation and it can inhibit neuronal hyperpolarization induced by GABA, an important inhibitory neurotransmitter, also enhancing neuronal responsiveness (43). Expression of opiate receptors involved in analgesia is also influenced by oestradiol, leading to increased neuronal responsiveness and possible hyposensitivity to opioids during the premenstrual period (57). Furthermore, oestradiol has an effect on CGRP, which is expressed in different regions of the brain and is involved in pain pathways. In the rat dorsal root ganglion, oestradiol has been shown to be able to increase CGRP synthesis (58).

The rise and fall of oestradiol levels might thus lead to imbalanced genomic and non-genomic effects in different brain structures, leading to increased neuropeptide release, neuronal excitability, and consequent migraine attacks (59).

Effects of oestradiol on vasculature

In addition to its neuronal effects, oestradiol affects the vasculature (60) and oestradiol itself can act as a vasodilator. Oestradiol-induced vasodilatation is caused by the release of nitric oxide (NO) after activation of the non-genomic phosphoinositide 3-kinase (PI3K) pathway (47). Oestradiol can also affect the vasodilatory response to other stimuli. In a rat model, CGRP release caused by electrical stimulation close to the dural artery, leads to increased maximal relaxation of this artery in rats treated with oestradiol versus rats treated with placebo (61). At the same time decreased levels of the vasoconstrictor 5-hydroxytryptamine (5-HT) were observed (62). In porcine coronary arteries the response to 5-HT decreased after physiological concentrations of oestradiol (63). However, the effects of oestradiol on the vascular system do not seem to be completely straightforward. For example, in a study of 60 women, increased NO pathway activation was observed during the late luteal phase of the menstrual cycle, when oestradiol levels rise, while migraine attacks

occur when oestradiol levels drop. This increased NO synthase activity, via activation of PI3K, can lead to an increase in NO release and thus increased vasodilation (64,65). Furthermore, a study was performed that compared dermal blood flow (DBF) responses after capsaicin application between women with MRM and healthy controls. DBF is a measure for the potency of the vessels of the skin to dilate. No difference in DBF was seen during the cycle in patients with MRM, but in healthy controls DBF was increased at day 1–2 of menstruation (48,49). These studies all point to an effect of oestradiol on the potency of a vessel to dilate and which is possibly increased before or at the start of menstruation; however, the results seem sometimes controversial and exact mechanisms still need to be discovered.

Progesterone

Progesterone levels also change during the menstrual cycle, during pregnancy, and the perimenopausal period (Figure 53.2). While progesterone is likely also involved in migraine pathophysiology, its effects can be synergistic, as well as antagonistic, compared to oestradiol.

The progesterone receptor is often co-localized with the oestrogen receptor and oestradiol can influence its expression in the brain (43). However, progesterone can lower oestrogen receptor expression (66). Progesterone levels are low during the follicular phase and increase during the luteal phase of the menstrual cycle (Figure 53.2). Increased urinary levels of progesterone metabolites were negatively correlated with migraine during the luteal phase of the menstrual cycle (15)]. The authors suggest a possible preventive effect of intermediate progesterone levels on migraine attacks. Where oestradiol has an excitatory effect on neuronal excitability via increased glutamate activity, progesterone can have an inhibitory effect via GABA-mediated chloride conductance (67). Furthermore, GABA receptor-induced decreased plasma protein extravasation in the trigeminal ganglion, as well as decreased c-Fos expression, is suggested to be involved in this protective mechanism (15,68,69). The progestins in the progestin-only oral contraceptives might thus also be involved in the decreased migraine frequency observed in some women using progestin-only oral contraceptives (19). However, the same authors showed that high levels of progesterone are also associated with worse migraine outcome. They suggest that there may be a turning point, after which progesterone is not beneficial anymore, but becomes a trigger (15). During pregnancy both progesterone and oestradiol levels are high (Figure 53.2), and it has been suggested that the new-onset migraine during pregnancy is more often MA, because of the combined excitatory effects oestradiol and progesterone can have on neuronal excitability and cortical spreading depression (42,70).

Genetics

Family studies show a heritability of approximately 40% for migraine (71,72), and a monogenetic inheritance pattern has only been identified for familial hemiplegic migraine. No specific inheritance study has been performed for menstrual migraine, but no differences in inheritance of total migraine are found between women and men (73). In a recent study, a relationship between *ESR1* (the gene coding for ERα) polymorphisms and migraine was found (74), although oestrogen receptors did not appear to have a prominent role in the genetics of migraine in a recent meta-analysis of genome-wide association studies in migraine (75).

Epigenetics

As oestradiol is known to be an epigenetic modulator, there may be a major contribution of epigenetic mechanisms. The methylene tetrahydrofolate reductase gene (*MTHFR*), encoding an important protein of the DNA methylation cycle, has been suggested to be involved in migraine (76,77), and mutations in this gene play a role in altered oestradiol synthesis by the ovaries (78). Moreover, the migraine prophylactic valproate inhibits DNA methylation and histone modifications, although no difference in effect is found between women and men (79). Thus, it may be possible that epigenetic changes of genes involved in migraine pathophysiology lead to the increased prevalence of migraine in women. A study in rats did not find changes in DNA methylation after treatment with oestradiol, but the authors indicated that this could be due to insufficient statistical power (80). Thus, more studies are needed to investigate the possible epigenetic effects of female hormones in migraine.

Treatment

From a hormonal point of view, migraine in female life has several milestones, each with specific treatment challenges. The focus will be on the treatment of migraine during menstruation, pregnancy and lactation, and menopause.

Menstrual migraine

Menstrual migraine may require a unique treatment approach. The pathophysiological background is different because of the premenstrual decrease of oestrogen or the change in the balance between progesterone and oestrogen. Attacks of menstrual migraine often break through otherwise effective preventive therapy, may be more severe, and are associated with a higher rate of recurrence (11). The relative predictability due to its cyclic nature provides an opportunity for pre-emptive preventive treatment.

Acute treatment

At first, attacks of menstrual migraine can be treated acutely in a manner similar to non-menstrual migraine. This is with non-specific drugs (analgesics, antiemetics, non-steroidal anti-inflammatory drugs (NSAIDs)) and specific migraine drugs (triptans, ergots). Triptans are the treatment of choice for those attacks that do not respond adequately to NSAIDS or other non-specific analgesics. Triptans used for the acute treatment of MRM attacks have been shown to be as equally effective as in their use for non-menstrual attacks and, in addition, control the nausea and vomiting associated with attacks (81). While 2-hour pain relief rates for MRM attacks treated with triptans are similar to non-MRM attacks, sustained response rates may be less because of the persistence of the trigger (low oestrogen levels and inflammation, prostaglandin synthesis) during menstruation. In such patients, specific drug combinations may be effective. In a randomized, double-blind, crossover study, the combination of rizatriptan 10 mg and dexamethasone 4 mg was superior for the 24-hour sustained pain-free end point (51% combination vs 32% rizatriptan alone; $P < 0.05$). In addition, the

sumatriptan–naproxen combination has also been shown to be effective in reducing the incidence of headache recurrence (82).

Short-term prevention

Short-lasting or intermittent prophylaxis is the daily use of acute medication starting shortly before and during the period of the anticipated trigger (the hormonal drop during menstruation). In menstrual migraine, medication could be taken during the 3–5 days before the start of menstruation and continued during the whole of the vulnerable time (Figure 53.3). If a patient is on a preventive, the dosage could be increased around the time of menstruation, but there are no rigorous data to support the efficacy of this practice (83).

Short-lasting prophylaxis with naproxen and magnesium has been described for that purpose. The most commonly used NSAID for perimenstrual migraine prevention is naproxen sodium 550 mg administered twice daily.

The most rigorous evidence for the use of triptans for perimenstrual prevention of migraine exists for zolmitriptan and frovatriptan. Zolmitriptan 2.5 mg twice or three times daily was demonstrated to be superior to placebo in a randomized, double-blind trial, reducing the mean number of headaches and the frequency (three times daily 58.6% ($P = 0.0007$); twice daily 54.7% ($P = 0.002$); placebo 37.8%) versus placebo (84). Frovatriptan (2.5 mg once or twice daily) significantly reduced migraine severity, duration, use of rescue medication, and the incidence of MRM by 67% and 52%, respectively, compared with placebo (41%) (85). Frovatriptan was started 2 days prior to the onset of menstrual flow and continued for 6 days. A second study in patients who had failed to respond to at least one previous triptan demonstrated efficacy with frovatriptan administered for perimenstrual prevention (86).

An evidence-based review identified six randomized controlled trials involving 633 participants who had received frovatriptan 2.5 mg once daily, 584 received frovatriptan 2.5 mg twice daily, 392 received naratriptan 1 mg twice daily, 70 received naratriptan 2.5 mg twice daily, 80 received zolmitriptan 2.5 mg twice daily, 83 received zolmitriptan 2.5 mg three times daily, and 1104 received placebo (87). Overall, all triptans were considered to be effective for the short-term perimenstrual prevention of MRM. Frovatriptan 2.5 mg twice daily and zolmitriptan 2.5 mg three times daily have the highest level of evidence, and only frovatriptan 2.5 mg twice daily received level A evidence and was determined to be effective for prevention of MRM, according to the American Academy of Neurology and American Headache Society joint guidelines (88).

Obviously, when using triptans as short-term prevention for migraine, the amount of medication used per month should not increase the recommended maximum to prevent medication overuse headache (89).

The efficacy of oral magnesium (360 mg of magnesium pyrrolidone carboxylic acid) was shown in a very small placebo-controlled, double-blind study of 20 women to decrease the severity of the premenstrual syndrome symptoms and the duration and intensity of MRM (90). Short-term prevention with ergot alkaloids, calcium antagonists, corticosteroids, and anxiolytics showed no effect. Diuretics, pyridoxine, and other vitamins were also ineffective (91).

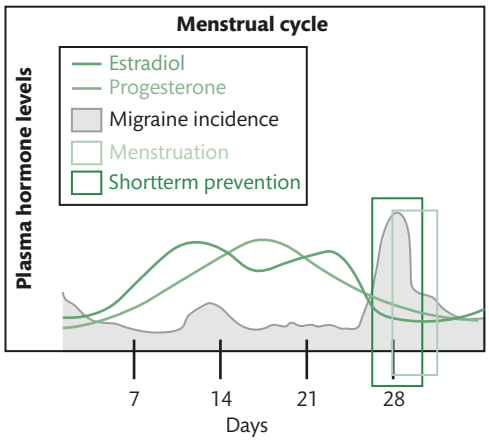

Figure 53.3 Window for short-term prevention of menstrual(ly related) migraine.

Adapted from Springer Nature, *Journal of Headache and Pain*, 13, 3, Sacco S, Ricci S, Degan D et al., Migraine in women: the role of hormones and their impact on vascular diseases, pp. 177–189, © 2012.

Hormonal treatment

Treatment with female hormones can be considered when the aforementioned treatments fail, but it is often disappointing. Progesterone is not effective when given alone. The concept of hormonal treatment is to achieve a constant plasma concentration of oestrogen. To avoid the first-pass effect through the liver, transdermal gel or patches are preferred to oral administration. These are to be administered 2–3 days before the expected first menstruation day, and to be replaced every other day until the end of the period (16,92). In a randomized, double-blind, placebo-controlled, crossover study, assessing the effect of perimenstrual oestradiol on menstrual attacks of migraine, transdermal oestradiol was associated with a 22% reduction of migraine days ($P = 0.04$) (93). In this study, oestradiol gel was applied from about day –6 of the menstrual cycle and continued until day 2 of the following menstrual cycle.

When combined oral contraceptive pills (COCP) are tried, migraine can become worse (in approximately 25%), stay the same (in approximately 50%), or become less frequent (in approximately 25%) (16). There are no significant differences between the different types of COCP, or the different dosages. Constant daily use of COCP, with no pill-free week, is a widely used method to prevent pill-free week migraine attacks. Women take the COCP on a daily basis for a period of 4–6 months. The monthly 'oestrogen withdrawal' effect will be prevented by this method and this can prevent an attack. Break-through bleeding with migraine attacks are, however, frequent. Coffee et al. (94) investigated the effect an extended 168-day COCP regimen in a randomized, double-blind, placebo-controlled, pilot study. Patients with a spontaneous menstrual cycle and patients with 21/7-day COCP, started with an extended 168-day of daily COCP (150 μg levonogestrel and 30 μg ethinyl oestradiol). Compared to baseline, the 168-day extended treatment period with COCP resulted in a decrease in average daily headache score from 1.29 to 1.10 ($P = 0.034$).

Migraine during pregnancy and lactation

As mentioned earlier, in 60–70% of pregnancies the frequency and intensity of migraine attacks lessens, especially in the second and third trimester. In a smaller percentage of pregnancies migraine continues to be bothersome or will even increase. Pregnancy poses limitations to the treatment of migraine. Anne MacGregor (95)

Table 53.2 Acute medication: use during pregnancy and lactation.

Drug	First trimester	Second trimester	Third trimester	Breastfeeding
Acetaminophen	✓✓	✓	✓	✓
Codeine	(✓)	(✓)	(✓)	✓*
Aspirin	(✓)	(✓)	A	A
Diclofenac	(✓)	(✓)	A	✓
Ibuprofen	(✓)	(✓)	A	✓
Naproxen	(✓)	(✓)	A	✓
Domperidone	(✓)	(✓)	(✓	✓
Metoclopramide	(✓)	(✓)	(✓)	(✓)
Prochlorperazine	(✓)	(✓)	(✓)	(✓)
Ergotamine	CI	CI	CI	CI
Almotriptan	ID	ID	ID	ID
Eletriptan	ID	ID	ID	(✓)
Frovatriptan	ID	ID	ID	ID
Naratriptan	?(✓)	?(✓)	?(✓)	(✓)
Rizatriptan	?(✓)	?(✓)	?(✓)	(✓)
Sumatriptan	?(✓)	?(✓)	?(✓)	✓
Zolmitriptan	ID	ID	ID	(✓)

CI, contraindicated; A, avoid; ID, insufficient data;?(✓), insufficient data, probably safe; (✓), damage not likely; ✓, no proof for damage. *In nursing mothers, the ultra-rapid conversion of codeine to morphine can result in high and unsafe levels of morphine in blood and breast milk. This is a very rare side effect of using codeine to treat pain or cough (114).

Adapted from *Journal of Family Planning and Reproductive Health Care*, 33, 2. MacGregor EA, Migraine in pregnancy and lactation: a clinical review, pp. 83–93. © 2007 with permission from BMJ Publishing Group Ltd.

published a review concerning the use of medication in different stages of pregnancy. Tables 53.2 and 53.3 are adapted summaries of her findings. In practice, most of the medication is used in the first trimester. Although the therapeutic dosage of most of the acute migraine medication in their normal range does not exceed the risk of malformation or miscarriage, it remains preferable to advise the safest options (96). For acute treatment, acetaminophen is safe during pregnancy. Aspirin and NSAIDs can be used with caution, but should be avoided after 30 weeks (97). NSAIDs (not aspirin) can be transmitted during breastfeeding. Domperidone is preferred to metoclopramide, but both can be used during pregnancy and breastfeeding. Sumatriptan has a US Food and Drugs Administration pregnancy category rating of C (i.e. animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women, despite potential risks). A recent meta-analysis of pregnancy outcomes following prenatal exposure to triptans from 1991 to 2013 identified one case–control study and five cohort studies that included information on duration of gestation, major congenital malformations, and spontaneous abortions of infants following prenatal triptan exposure. These studies included 4208 infants of women who used sumatriptan or other triptan medications, and 1,466,994 children of women who did not use triptans during pregnancy. No significant increases in rates for major congenital malformations, prematurity, or spontaneous abortions were found when comparing the triptan-exposed group to the migraine and no triptans control group (odds ratio (OR) 0.84, 95% confidence interval (CI) 0.61–1.16; OR 0.90, 95% CI 0.35–2.30; OR 1.27, 95% CI 0.58–2.79, respectively). There were no increased rate of major congenital malformations (MCMs; OR 1.18, 95% CI 0.97–1.44) or prematurity (OR 1.16, 95% CI 0.67–1.99) when the triptan-exposed group was compared with the healthy controls. However, there was a significant increase in the rates of spontaneous abortions (OR 3.54, 95% CI 2.24–5.59). When the migraine no-triptan group was compared with healthy controls, a significant increase in the rates of MCMs was found (OR 1.41, 95% CI 1.11–1.80). The conclusion of this meta-analysis was that the use of triptans during pregnancy does not appear to increase the rates for MCMs or prematurity, but that the increased rates of spontaneous abortions in the triptan-exposed group and the increased rates of MCM in the migraine no-triptan group requires further research (98). Recently, the final results of a 16-year worldwide pregnancy registry of sumatriptan, naratriptan, and treximet were published (99). The registry included 680 exposed pregnant women, which resulted in 689 infants and fetuses, further defined as outcomes. Of these outcomes, 626 were exposed to sumatriptan, 57 were exposed to naratriptan (seven were exposed to both sumatriptan and naratriptan), and six were exposed to the sumatriptan/naproxen sodium combination product. The estimated risk of major birth defects following first-trimester sumatriptan exposure is 4.2% (n = 20/478, 95% CI 2.6–6.5). Among 52 first-trimester exposures to naratriptan, major birth defects were reported in one outcome, an infant with exposure to both sumatriptan and naratriptan (birth defect risk of 2.2%; n = 1/46, 95% CI 0.1–13.0%).

Sumatriptan can be used during breastfeeding, and the same is probably true for the other triptans with a low bioavailability and low absorption by the baby, like zolmitriptan, rizatriptan, and eletriptan (100) (Table 53.4). Removing the mother's milk in the 4 hours after triptan intake sufficiently reduces its absorption by the baby (101). Ongoing frequent attacks can be treated with propranolol, which has the best safety profile for prophylaxis during both pregnancy and lactation (102).

Table 53.3 Prophylactic medication: use during pregnancy and lactation.

Drug	First trimester	Second trimester	Third trimester	Breast feeding
Amitriptyline	(✓	(✓)	(✓)	(✓)
Aspirin, low dose	(✓)	(✓)	A	A
Atenolol	A	A	A	(✓)
Gabapentin	?(✓)	?(✓)	?(✓)	ID
Methysergide	ID	ID	ID	ID
Metoprolol	(✓)	(✓)	(✓)	✓
Pizotifen	ID	ID	ID	ID
Propranolol	(✓)	(✓)	(✓)	✓
Topiramate	ID	(✓)	(✓)	ID
Valproate	CI	ID	ID	✓
Verapamil	(✓)	(✓)	A	✓

CI, contraindicated; A, avoid; ID, insufficient data; ?(✓), insufficient data, probably safe; (✓), damage not likely; ✓, no proof for damage.

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Table 53.4 Pharmacokinetics triptans.

Parameter	Almotriptan	Eletriptan	Frovatriptan	Naratriptan	Rizatriptan	Sumatriptan	Zolmitriptan
Oral bioavailability (%)	69	50	26–30	63–74	40	14	40
$T_{1/2}$ (h)	3.5	5	25	5-6.3	2	2	3
T_{max} (h)	2–3	1.5–3	3	2–3	1	2–2.5	2–4

Menopausal phase ('puberty in reverse')

While the prevalence of migraine decreases with the increase of age, the attack frequency of migraine often increases once more in the period before or around the menopause (average age of the last bleeding is 51 years), only to improve after that (Box 53.1) (103). Women appear to go through puberty again, but in reverse order. The postmenopausal improvement is likely explained by the lower oestrogen levels and high follicle-stimulating hormone levels (38). The disappointment of this perimenopausal aggravation should be explained with emphasis on the often temporary nature of the increase of migraine. An acute or preventative regime needs to be prescribed temporarily (104). To diminish perimenopausal complaints (i.e. vasomotor symptoms and sleep disturbances) and to prevent long-term health effects of menopause before the age of 45 years (i.e. premature cardiovascular disease and sexual dysfunction), hormone replacement therapy (HRT; oral or transdermal conjugated oestrogens combined with cyclical oral progestogen) is often prescribed. Owing to the varying results of studies on migraine and HRT, it is difficult to determine the effect of HRT on migraine during the perimenopause. Studies have shown HRT to both to improve, as well as to worsen, migraine in perimenopausal women (105). At present, few data on the various regimens and types of HRT as a possible approach to prevent migraine during the menopause transition are available (103).

In postmenopausal women from the Women's Health Study, current HRT use was associated with higher risk of migraine than non-use (OR 1.42, 95% CI 1.24–1.62), both for users of oestrogen alone (OR 1.39, 95% CI 1.14–1.69) and users of oestrogen plus progestin (OR 1.41, 95% CI 1.22–1.63) (106). The Norwegian HeadHUNT study resulted also in an association between migraine and current use of HRT (OR 1.6, 95% CI 1.4–1.9) (107). However, in a survey performed by MacGregor et al. (108) in perimenopausal and postmenopausal women, a trend toward greater improvement of migraine in women using transdermal oestrogen versus oral conjugated oestrogens was shown.

After menopause: in 65% migraine decreases, in 10% it worsens, and in 25% it remains the same.

Box 53.1 Some data on the relationship between pregnancy and migraine

- Fewer attacks in 60–70% of patients.
- Temporary increase in the first quarter.
- Average time to first ovulation after delivery:
  - 189 days during breastfeeding;
  - 45 days in bottle feeding.
- Migraine is back in the first month postpartum:
  - 100% with bottle feeding
  - 44% with breastfeeding
- Decrease of migraine in both the second trimester of pregnancy and the first 3 months postpartum.
- Lactation and pregnancy seem to protect against migraine.
- After menopause: in 65% migraine decreases, in 10% it worsens, and in 25% it remains the same.

Hysterectomy and ovariectomy as treatment for menstrual migraine?

Neither hysterectomy nor oophorectomy have shown any improvement in hormonal migraine (109,110). Women suffering from severe menstrual migraine may ask for this type of treatment. The normal menstrual cycle is the result of the precise interplay of the various structures in brain and body involved in the hormone secretions. The removal of one organ from this complex system has little effect on the hormonal fluctuations of the menstrual cycle, although this may stop the menses. Surgery, neither hysterectomy nor ovariectomy, has not shown any efficacy. Gonadotropin-releasing hormone (GnRH), also known as luteinizing hormone-releasing hormone, is a tropic peptide hormone responsible for the release of follicle-stimulating hormone and luteinizing hormone from the anterior pituitary. Chemical ovariectomy with drugs like GnRH analogues to suppress ovulation has shown some effect. However, side effects of this drug-induced menopause are frequently listed and related to the induced hypo-oestrogenism: hot flushes, irritability, sleep problems, vaginal dryness, and headache. Some doctors only advise hysterectomy and ovariectomy in patients with untreatable menstrual migraine who have already responded well to chemical ovariectomy. These claims have an insufficient scientific base, so gynaecological operations like this should be discouraged.

However, GnRH agonists may be used as the last resort, but then supplemented with oestrogens (111). Goserelin (Zoladex) is a synthetic GnRH analogue, with which good results have been described in certain cases.

When prescribing hormonal treatments, we must carefully consider possible contraindications, such as MA, migraine attacks treated with ergotamine, a history of stroke or ischaemic heart disease, or other risk factors for thrombosis (112,113).

Conclusion

Oestradiol plays an important role in the increased migraine prevalence of women compared with men, but there is possibly also a role for progesterone (70). In particular, the drop in oestradiol levels before menstruation and after delivery, as well as the increased fluctuations perimenopausally, are thought to trigger mechanisms leading to migraine attacks (14,24). More research is needed to elucidate the exact mechanisms and pathways behind it. Although an effect of oestradiol on epigenetic changes in genes involved in migraine pathophysiology has not yet been established, both oestradiol and

CGRP are involved in epigenetic mechanisms and thus oestradiol might also affect migraine in an epigenetic manner.

Specific treatment of migraine in relation to female hormones is currently mainly based on consensus instead of real evidence. Hopefully, in the future, better treatment options with established efficacy will be available.

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54

Headache and the weather

Guus G. Schoonman, Jan Hoffmann, and Werner J. Becker

Introduction

There is a widespread belief that weather and other atmospheric factors can have a negative effect on health, in general, and headache, in particular. When studying the association between weather-related variables and headache a few questions arise: (i) What is weather? (ii) Do patients think weather is a trigger factor for headache? (iii) Are there any objective prospective studies and is it possible to quantify a possible association between variables and headache? (iv) What are the difficulties in studying the relation between weather and headache?

Firstly, what is weather? Is it just the variables that are presented in your daily weather report? In general, meteorological data consist of temperature, wind, barometric pressure, and humidity (Table 54.1). For this chapter, it was decided to include both classic weather-related variables, as well as other atmospheric factors, such as air pollution, altitude, diving, and electromagnetism (EM). An association between headache and the weather has long been suspected. Headache patients commonly report weather changes as a trigger factor for their attacks. In a diary study 35% of migraine patients and 18% of other headache patients suggested an association between weather and headache (1). Other studies found that up to 71% of headache patients might be weather-sensitive (2). A number of studies tried to confirm this clinical observation and to dissect specific weather parameters responsible for such an association, but the results have been inconclusive. The most frequent parameters investigated in a clinical setting are atmospheric pressure, temperature, and relative humidity. Next, the existing clinical evidence will be reviewed, as well as the pitfalls of past clinical research efforts that aimed to elucidate the association between headache and weather.

Weather and headache in general

The influence of meteorological factors on the initiation and maintenance of headache was described well before the publication of the first edition of the International Headache Society's (IHS) International Classification of Headache Disorders (ICHD) in 1988. As a result, initial studies aimed at elucidating the relationship between certain weather parameters and headache without differentiating between the different types of primary headaches. The results of these studies are largely inconclusive. For example, Schulman et al. (3) conducted a clinical trial on 75 headache patients and correlated their mean daily headache score with barometric pressure over a time period of 1 month. The results suggested that barometric pressure appears to have little, if any, effect on headache. In contrast, the results of another study suggested that higher ambient temperature and lower barometric pressure lead to an increased headache risk (4). However, as the pathophysiology of primary headaches differs substantially, it is unlikely that weather parameters have the same influence on all types of primary headaches. Therefore, results of these studies have to be interpreted with caution and have minimal, if any, clinical significance (Figure 54.1).

Tension-type headache and cluster headache

Most of the weather-related health studies have been conducted in migraine patients (see 'Weather and migraine'). The data on tension-type headache (TTH) and cluster headache are very limited. Clinical, population-based, and epidemiological studies have revealed a relationship between TTH and the weather (1,5–7). In these studies the estimated extent of the influence of weather as an aggravating factor of TTH varies significantly. While Rasmussen (5) reported that 26% of the male and 28% of the female participants with TTH indicate weather as a precipitating or aggravating factor in TTH, Spierings et al. (6) showed that 47% of patients with TTH report weather as an aggravating factor. Data on a correlation between cluster headache and weather is scarce. Only a few clinical studies have suggested a relationship, but further studies are needed to confirm this (8,9).

Weather and migraine

A substantial proportion of migraine patients claim to be weather-sensitive. In this context patients report that certain weather features, and especially certain weather changes, can trigger and aggravate their attacks. Consequently, a multitude of studies have investigated the relationship between the weather and migraine. As it became clear that patients' reports are not easily reflected in the results of structured clinical studies, several approaches have been developed to prove the link between migraine and weather. Even so, the relationship has not yet been completely elucidated.

In 1968, Barrie et al. (10) conducted a clinical trial testing the efficacy of ergot derivatives for the treatment of migraine. In order to exclude potential confounding factors the authors tested if a

Table 54.1 Common weather variables and other atmospheric factors included in this chapter.

Subgroup	Variables
Meteorological	Temperature, barometric pressure, wind, sun, cloud cover, precipitation, visibility
Air pollution	PM10, PM2.5, ozone, carbon monoxide, sulfur dioxide, nitrogen dioxide
High altitude	Oxygen partial pressure, barometric pressure
Diving	Ambient pressure
Electromagnetism	Electromagnetic waves (see Figure 54.4)

PM10, particulate matter with an aerodynamic diameter of ≤ 10 μm; PM2.5, particulate matter with an aerodynamic diameter of ≤ 2.5 μm.

correlation between migraine prevalence and meteorological variables existed. No such correlation could be observed for maximum and minimum wind speed, barometric pressure, relative humidity, temperature, rainfall, and hours of sunlight. In line with these results, a clinical trial conducted by Wilkinson et al. (11) also failed to prove a link between weather and migraine, although this trial only considered weather as such, without differentiating further among specific weather parameters. In contrast, Osterman et al. (12) demonstrated a significant correlation between migraine frequency, atmospheric pressure, and temperature. The results of another study of 44 migraineurs indicate that low barometric pressure, as well as a significant rise in barometric pressure, may be associated with a reduced migraine frequency (13). Given that all these trials were conducted prior to the publication of the first edition of ICHD, the results have to be interpreted with caution as the groups of migraineurs included in these studies may not have been very homogenous or comparable.

A few years later, following the publication of the diagnostic criteria by the IHS, a series of studies addressed the potential relationship between weather and migraine. In a large cross-sectional epidemiological study weather changes were identified as precipitating factors of migraine (5). These results were largely confirmed by three retrospective studies (6,14,15). Interestingly, in the study by Rasmussen et al. (5), the influence of weather on migraine was significantly less than on TTH, in contrast to the results from other studies. Given that all of these studies analysed headache data retrospectively by a structured questionnaire or telephone interview, potential confounding factors resulting from a retrospective subjective report have to be considered. Furthermore, the incidence of migraine was only correlated to weather or weather changes as such, not to specific weather parameters such as atmospheric pressure, temperature, or relative humidity. Therefore, the clinical significance of these results is limited.

Recent studies were commonly designed in such a way as to take into consideration the shortcomings of previous trials, as these commonly led to a questionable clinical significance of the results. Therefore, studies aimed to correlate only specific weather parameters to migraine over extended observational periods. Even so, the results have been inconclusive and a specific weather parameter responsible for the influence of weather on migraine, if at all existent, remains largely unknown. In this context, Larmande et al. (16) conducted a large prospective study over a 1-year period. The

Figure 54.1 Red sky predicting low headache risk?

Red sky over the Commewijne river in Suriname. In some countries this is considered a good forecast: 'Red sky at night, shepherd's delight. Red sky in the morning, shepherd's warning.' Whether it is a delight for headache patients is uncertain.

Courtesy of Guus G. Schoonman.

study failed to demonstrate a correlation between temperature; wind; atmospheric pressure; rain; sunshine; relative humidity; icy, stormy, or foggy weather; or their relative changes and the onset of migraine attacks. Zebenholzer et al. (17) conducted a well-designed large prospective, diary-based cohort study in 238 migraineurs over 3 months, to analyse the potential of specific meteorological variables as a trigger factor for migraine attacks. The variables investigated included air temperature, atmospheric pressure, relative humidity, wind speed, sunshine duration, and precipitation. None of these parameters showed a statistically significant correlation questioning the clinical importance of specific weather factors on migraine (17). Another interesting approach to assess a possible link between meteorological variables and migraine was used in a clinical study conducted by Villeneuve et al. (18). The study examined the association between emergency room visits and the meteorological conditions within the 24 hours preceding the visit. The study used a case crossover design and included 4039 emergency room visits in the evaluation. A significant relationship between temperature, relative humidity, and atmospheric pressure and the number of emergency visits could not be found.

In contrast to these results, other studies did observe correlations between specific variables and migraine. Prince et al. (19) conducted an interesting study on 77 migraineurs to assess the patients' belief of weather being an influential factor in triggering migraine attacks and to retrospectively assess the objective correlation between the meteorological variables of temperature, relative humidity, and atmospheric pressure and data on migraine incidence obtained from headache diaries. The results indicated that temperature and relative humidity, as well as—to a lesser extent—atmospheric pressure serve as a precipitating factor for migraine attacks. In a complex study conducted by Hoffmann et al. (20), data from headache diaries recorded in 4-hour time frames over a 1-year period were correlated to temperature, relative humidity, and atmospheric pressure obtained in the same 4-hour steps. The relative changes of weather parameters were also considered. The long observational period was chosen to exclude a possible bias that may be caused by seasonal differences in migraine incidence. The results indicated that lower air temperature and higher relative humidity are correlated with the occurrence of a migraine attack. These results were confirmed in another study using a different study design (21). Perhaps the most interesting result of the study conducted by Hoffmann et al. (20) is the fact that only a subgroup of the included migraineurs was highly sensitive to specific meteorological conditions, whereas the majority of included migraineurs did not appear to be weather sensitive. Notably, a substantial correlation with atmospheric pressure was not seen. In contrast, Kimoto et al. (22) analysed the influence of atmospheric pressure on migraine incidence in Utsunomiya, Japan, using a very similar study design. Interestingly, the authors observed a significant correlation in that changes in atmospheric pressure were associated with an increased incidence of migraine attacks.

Despite the fact that most studies have focused on temperature, relative humidity, and atmospheric pressure as potential trigger factors, other weather variables may also have a significant involvement. In this context, two Canadian studies investigated the influence of chinook winds, which occur in the southern part of the province of Alberta in Canada, in increasing the probability of a migraine attack (23). Chinook winds were defined in the study as warm winds with a wind direction of south-southwest to west-northwest, with a wind velocity above 15 km/hour that lead to an abrupt increase in ambient temperature of over 3°C within 1 hour. The results of the larger study show that, in contrast to their own perception, most of the patients were not sensitive to chinook winds. However, a subgroup of patients was, indeed, weather sensitive, with a higher risk of a migraine attack on a chinook day. Interestingly, another subset of patients was chinook sensitive on the preceding day, but only two of the 75 patients were weather sensitive on both pre-chinook and chinook days. Which weather parameter associated with chinook winds is responsible for triggering migraine attacks in susceptible individuals is unclear.

Finally, the exposure to sunlight has been demonstrated to correlate with the incidence of migraine (24). An interesting study conducted in an Arctic population in northern Norway revealed that a subgroup of migraineurs appears to be susceptible to sunlight-induced migraine attacks, as this subgroup had a higher incidence of migraine during sunny days (25). Furthermore, this subgroup showed an annual periodicity with an increase in incidence during the light-intensive summer months versus the winter months of polar night. Similar results have been reported in previous studies (26), as well as in a series of case reports of migraineurs that after moving into the arctic environment developed the same periodicity (27).

The pathophysiological basis of the meteorological influence on migraine is largely unknown and experimental and preclinical data on this subject are scarce. It is not clear which neuronal structure might sense the meteorological change and trigger an increase in neuronal activity within the trigeminal system. Messlinger et al. (28) conducted a series of well-structured in vivo experiments, which demonstrated that neurons within the trigeminal nucleus caudalis with afferent input from the eye respond with a neuronal facilitation to lowering of atmospheric pressure. Meningeal afferents appeared to play a minor role in atmospheric pressure-induced increase of neuronal activity (28). However, the involved group of neurons with ophthalmic afferents had convergent input from the meninges explaining the connection to meningeal nociception and the generation of headache. The results support the clinical observation that a decrease in ambient temperature and an increase in relative humidity, increases the incidence of migraine (20), as these changes are linked to a reduced atmospheric pressure. Similar experimental approaches are needed to elucidate the influence of other meteorological variables on neuronal activity to improve the understanding how the weather may influence migraine.

Taken together, several meteorological variables have been identified to increase the risk of a migraine attack, although their influence appears to be rather weak. Clinical evidence suggests that the change in certain parameters, rather than their absolute values, may be the responsible influential factor. Moreover, it may be speculated that the meteorological influence as such is not capable of triggering a migraine attack but may increase the susceptibility for its initiation.

Other atmospheric conditions in relation to headache

Besides the standard weather variables there are several other atmospheric conditions that have been linked to headache (Table 54.1). These different factors will be discussed in the following subsections.

Air pollution and indoor air quality

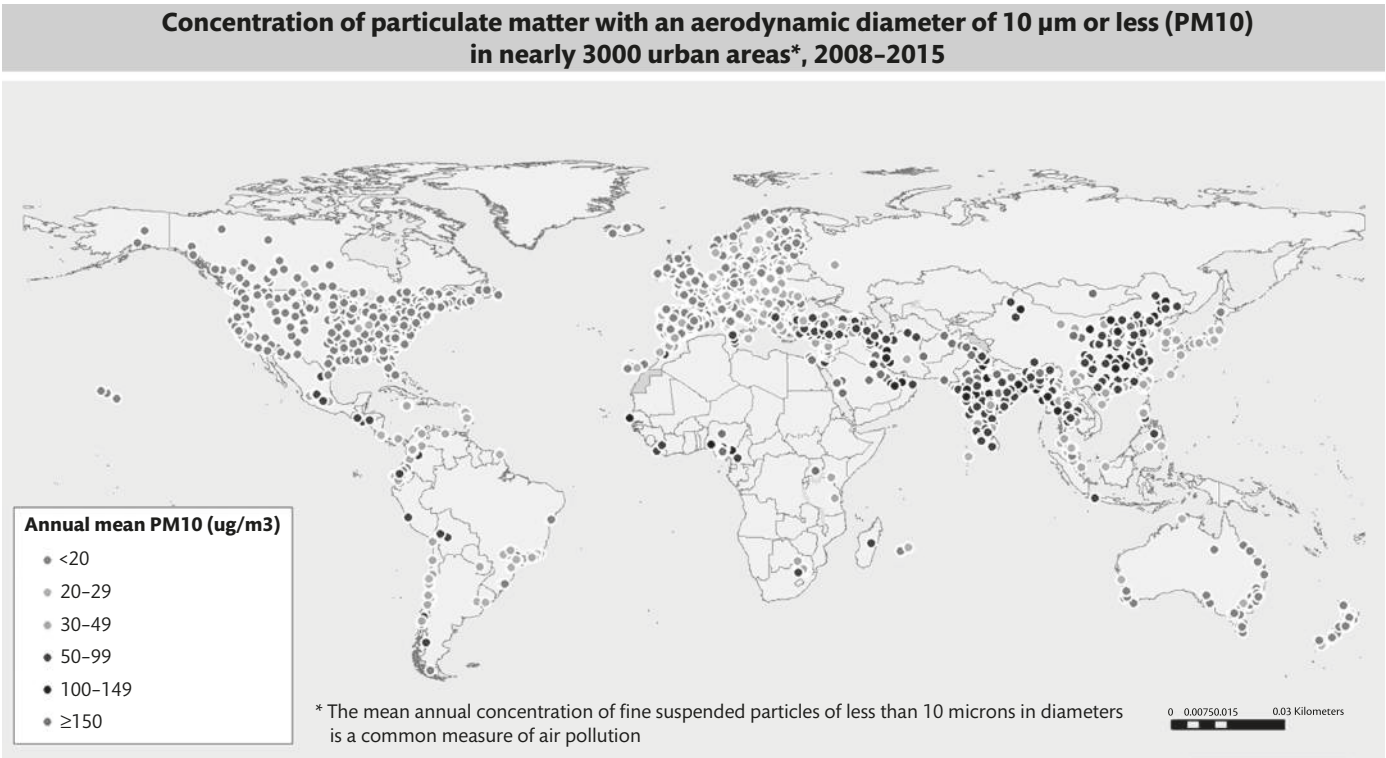
Normal air consists of around 78% nitrogen, 21% oxygen, 0.9% argon, 0.04% carbon dioxide, and a small amount of other gases. Ambient air also contains a variable amount of water—on average, around 1%. The standard atmospheric pressure is 1013.25 millibars. In urban environments the air can become polluted with all sorts of small particles and molecules. Several studies have assessed the relation between air pollution and headache. A large-scale study of 7054 emergency visits in Boston, USA, for headache did not find a difference between the level of air pollution (fine particulate matter, black carbon, nitrogen, and sulfur dioxides) in the 24 hours preceding the emergency room visit and at a random control day (4).However, three other studies in Canada, Chile, and Italy found a positive relation between air pollution and headache (29–31). Possibly, there is a dose–effect relation as the level of pollution was much higher in the Chilean study than in the Boston study (Figure 54.2). Also, adverse indoor air conditions can cause headache complaints (32).

High-altitude conditions

With increasing altitude the atmospheric pressure decreases. The percentage of oxygen remains constant at around 21%, but the partial oxygen pressure decreases, causing hypoxia (Figure 54.3). High-altitude exposure can cause acute mountain sickness with headache as one of the main symptoms (33). The incidence of headache at an altitude of 2200–3817 m was 31% (34) and rose to 87% an altitude of 5671 m (35). It is suggested that there are three types of headache at altitude: (i) as part of acute mountain sickness; (ii) headache independent of mountain sickness; and (iii) altitude-triggered migraine (36). Risk factors for headache at altitude are a history of migraine, low arterial oxygen pressure, exertion, and low fluid intake (34). Hypoxia has been shown to induce migraine in susceptible patients under experimental conditions (37). Altitude-related headache that is not related to migraine seems to respond to oxygen therapy within 15 minutes, in contrast to migraine headache (38)

Diving and headache

Scuba diving is a common recreational sport. For every 10 m of submersion an extra 1 atmospheric pressure is added to the ambient pressure. The volume of gas is inversely related to the pressure and upon ascent it is important to release all inhaled to gases to prevent the formation of gas bubbles in various tissues (39). Diving can cause a whole range of medical problems, headache being one of them. When a diver develops headache during or after a dive it is important to make sure it is not a secondary headache related to decompression sickness or any other diving-related trauma (40). Whether diving is a trigger for primary headache disorders like TTH and migraine is not completely clear. In a case–control study comparing divers with controls it was suggested that diving does not increase the frequency of headache (41).


Concentration of particulate matter with an aerodynamic diameter of 10 µm or less (PM10) in nearly 3000 urban areas*, 2008–2015
Annual mean PM10 (ug/m3)
<20
20–29
30–49
50–99
100–149
≥150
* The mean annual concentration of fine suspended particles of less than 10 microns in diameters is a common measure of air pollution
0 0.00750.015 0.03 Kilometers

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whalsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of ils frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Figure 54.2 (see Colour Plate section) Exposure to particulate matter with an aerodynamic diameter of ≤ 10 µm (PM10) in 1100 urban areas, 2003–2010.

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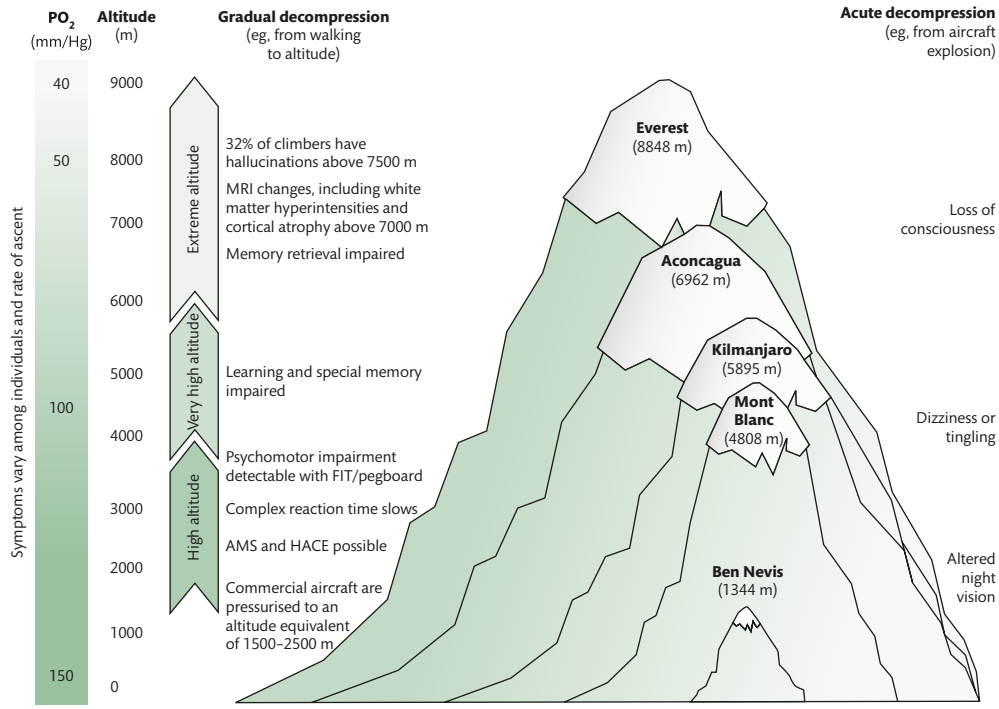

Figure 54.3 Altitude and neurological consequences.

The relation among altitude, the partial pressure of oxygen, and the neurological consequences of acute and gradual exposure to these pressure changes.

MRI, magnetic resonance imaging; PO2, partial pressure of oxygen; AMS, acute mountain sickness; HACE, high-altitude cerebral oedema; FTT, finger-tapping test.

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Electromagnetism

The human body is exposed to different kinds of electromagnetic fields such as mobile telephones and high-voltage overhead power lines (Figure 54.4). Between 1.5% and 5% of the population report hypersensitivity to electromagnetic fields causing symptoms like headache, dizziness, and anxiety (42). Several sources of EM have been studied in observational studies for their headache-triggering capacity. For instance, very-low-frequency atmospherics (sferics) are alternating electric and magnetic fields that originate from electrical atmospheric discharges commonly known as lightning. This meteorological phenomenon is subject to an annual periodicity with a peak during seasons of high thunderstorm activity. Results of several small studies indicate that a correlation between the occurrence of sferics and the incidence of migraine may exist (43,44). In line with these studies, results of a recent observational cohort study suggest a relationship between the occurrence of lightnings and migraine frequency (45). However, these findings are based on small patient numbers and therefore require larger studies to be confirmed. Another study investigated the incidence of headache and migraine in three communities in Cyprus, of which two were exposed to the high-frequency waves of a military antenna. The exposed communities reported significantly more headache and migraine (46). However, a meta-analysis including 22 observational studies did not find evidence for a significant association between EM and headache (47). This is in accordance with a provocation trial of 17 EM-sensitive patients, which did not find an association between the use of mobile phones and headache (48). The aforementioned studies suggest that there is limited evidence of electromagnetic fields causing headache. Whether EM fields are able to trigger migraine or TTH in susceptible patients has never been studied, to the best of our knowledge.

Difficulties in studying the association between weather and headache

Migraineurs commonly mention the weather as a trigger factor for their attacks. In fact, it is frequently reported as one of the main trigger factors. Nevertheless, clinical studies have significant difficulties in proving this relationship. Having said that, it is unlikely that a substantial number of migraineurs are subject to a misperception. Therefore, finding an adequate study design that may reflect the patients' perception can be challenging.

Initial studies were hampered by the lack of standardized criteria. Therefore, subtle differences could not be assessed in an adequate way as the included group of patients was not sufficiently homogenous. Furthermore, initial studies occasionally studied the influence of weather or its specific variables on headache without differentiating further between the different primary headaches. As the pathophysiological mechanisms and trigger factors of primary headaches differ substantially, the clinical significance of these results is highly questionable. Finally, these studies frequently investigated the influence of weather as such, not the influence of a certain weather parameter. Given that only a few variables are likely to have

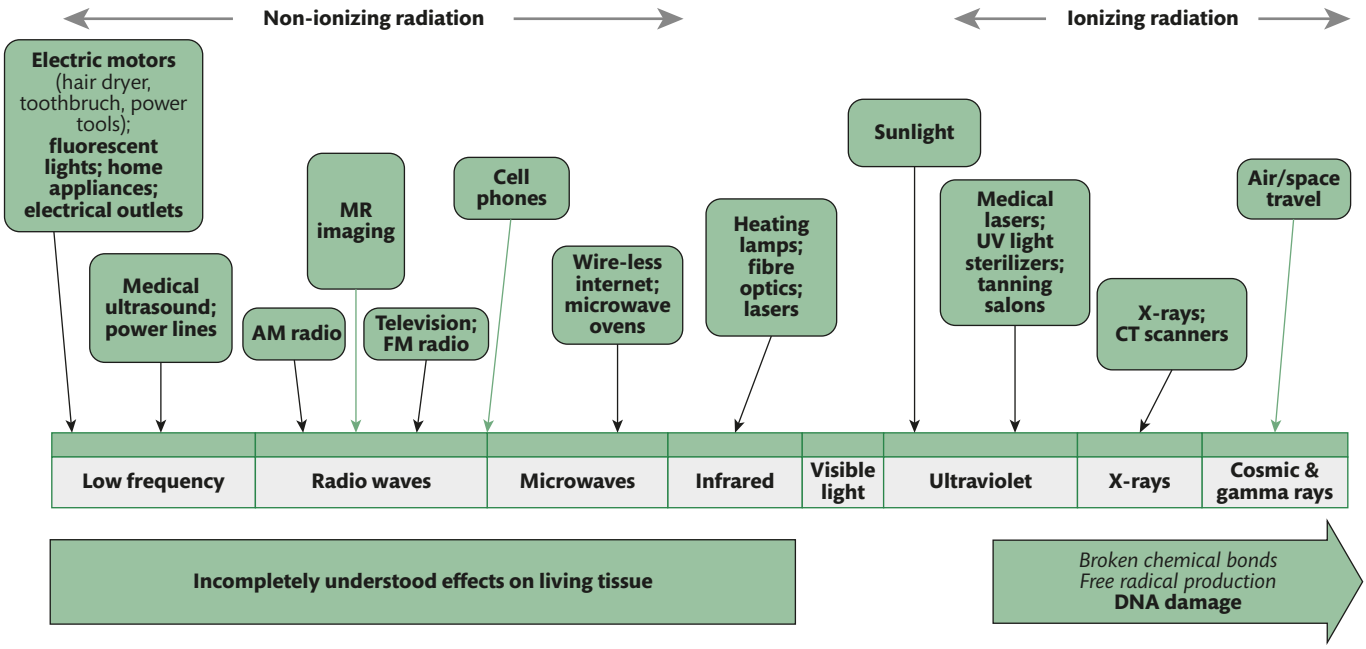

Figure 54.4 The electromagnetic spectrum.

MR, magnetic resonance; CT, computed tomography.

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an influence on the pathophysiological mechanisms of migraine, the approach of investigating the influence of weather is too broad and it may be expected that results are inconclusive.

One of the most common study designs to investigate triggers factors of a migraine attack is a patient survey. In most cases, data acquired with a survey are collected retrospectively. However, studies on the influence of the weather on migraine are characterized by a remarkable discrepancy between the subjective perception of weather sensitivity and the objective study results. In the clinical study conducted by Cooke et al. (23), which aimed to investigate the influence of chinook winds on the incidence of migraine, 88% of the migraineurs included in the study reported that chinook winds influenced their migraine. However, only 39% of the migraineurs that felt chinook-sensitive actually were chinook-sensitive. Similar observations were made in another clinical study in which 62% of migraineurs believed themselves to be weather-sensitive, but in only 51% of patients this was objectively confirmed (19). Therefore, in this context patient surveys are subject to a significant bias.

Even if studies are based on more objectively acquired data they have significant difficulties in reflecting the experience commonly reported by migraineurs. Several reasons may account for this discrepancy. Firstly, clinical evidence indicates that not all migraineurs are weather-sensitive (20). In fact, this may only be the case in a fairly small subgroup of patients (19,20,23). Therefore, if the influence of meteorological factors is investigated on a randomly selected group of migraineurs, a probable relationship in a subgroup of migraineurs may lose its significance in the complete study group. Secondly, it is unlikely that a meteorological influence as such triggers a migraine attack. A specific meteorological condition may increase the risk of a migraine attack in susceptible individuals, but other factors are probably still required to trigger an attack. This may be a genetic predisposition, stress, sleep deprivation or any other condition known to increase the susceptibility for the triggering of a migraine attack. Therefore, even if meteorological conditions are favourable for triggering a migraine attack, this does not necessarily mean that an attack will actually initiate. However, if the attack does not initiate, the favourable meteorological condition will remain undetected.

Finally, statistical peculiarities have to be considered for an appropriate study design. Firstly, meteorological variables commonly do not change independently. For example, if atmospheric pressure falls, temperature falls, and relative humidity increases owing to the higher probability of precipitation. Consequently, it may be difficult to dissect which of the variables is responsible for an observed correlation. Secondly, this kind of study requires a long observational period and several daily data points to exclude a potential bias due to seasonal differences or variations in a single day. For example, migraine attacks are likely to occur in the early-morning hours (20). Therefore, if a certain condition is present at a certain time and a correlation is observed, this correlation needs to be appropriately corrected for daytime in order to allow an adequate conclusion on whether the attack is resulting from an increased risk resulting from a specific meteorological condition or a specific time of the day. Long observational periods and frequent data points may lead to the accumulation of a substantial amount of data. However, the more data points are acquired, the easier it becomes to achieve statistical significance without any associated clinical significance. Consequently, appropriate statistical corrective measures have to be used to account for these problems and statistical significances have to be critically analysed for their clinical significance. Finally, a possible time lag has to be considered. It is unlikely that a certain meteorological condition immediately leads to a clinical consequence, in

this case a migraine attack. As a result, correlations should not only consider a certain weather variable and a co-existent migraine incidence, but also consider meteorological conditions that were present at least in the preceding 2 days. This is especially important from a pathophysiological point of view as a migraine attack is likely to start long before the actual migraine pain initiates, as the premonitory symptoms of a migraine attack can precede the headache by up to 48 hours (49).

Conclusion

The role of weather changes or specific weather patterns in triggering headache or migraine attacks remains an area of controversy. Up to 71% of patients believe that there is an association between their headache attacks and weather-related variables (2). However, objective prospective studies are mainly negative or, at best, show a very modest effect. Of the non-weather atmospheric variables only high altitude is an important trigger, causing headache in up to 87% of patients. It is difficult to imagine that the observation of numerous individuals with migraine worldwide that weather changes are a significant migraine trigger for them is not based on reality. Whether patients with migraine are somehow being misled by confounding factors, or whether current research methodologies are not sufficient to show objectively the relationship between many weather conditions and migraine attack onset, remain to be determined.

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55

Headache and sport

David P. Kernick and Peter J. Goadsby

Introduction

Headache is a common problem with a 3-month prevalence in the UK of 70% (1). Migraine alone affects 7.6% of males and 18.3% of females (2), and this is likely an underestimate. Despite a substantial impact, the needs of many people with headache are unmet (3,4). On a worldwide basis, headache problems rank at the very top of neurological causes of disability (5).

Headache can have an impact on sport or physical activity, either coincidentally or as a direct result of participation. For the professional sportsperson there are important implications for performance and management, with a number of headache medications being restricted. At a population level, 2% of people have given up sports-based exercise due to headache (6). Against a background of initiatives to encourage activity in the population, it is important to identify and understand any factors that may inhibit this pursuit. Physical activity is associated with a reduced risk of a wide range of illnesses that include coronary heart disease, obesity, and type 2 diabetes (7). Regular resistance training can also lower blood pressure, improve glucose metabolism, and reduce cardiovascular disease risk (8). It is estimated that in the UK, ill health attributable to physical inactivity costs the National Health Service more than £1.06 billion per year and is directly responsible for more than 35,000 deaths every year (9).

The mechanisms causing headache during activity are poorly understood but can include direct activation of dural pain fibres, central activation of trigeminal pain pathways, radiation from facial or neck structures, or from dysfunction of brain centres normally concerned with sensory modulation. Microscopic damage incurred as a result of shearing or acceleratory forces are also likely to be important in the sports setting.

The beneficial impact of sport and aerobic exercise on headache remains contested. However, against a background of policy initiatives to increase activity and the fact that headache sufferers may be less active (10), an understanding of the relationship between sport and headache and options for management is important for healthcare practitioners at all levels.

Epidemiology of sport and exercise-induced headaches

Estimates of the prevalence of exertional headache range between 12% and 30% (6,11). Moreover, the distinction between primary exercise headache and headache, such as migraine, triggered by exertion is often not well delineated. It is particularly prevalent in adolescents, who are often the focus of exercise initiatives. Sports-related headaches are likely to be more common in headache-prone individuals who experience other types of primary headache, particularly migraine.

The prevalence of headache specifically related to sport is not well described. A study of university students found that 35% experienced sports or exercise-related headaches (12). A study of Australian Football League players, where contact and propensity for mild head trauma must be high, found that 49% of respondents reported headache during competitive play and 60% during training (13). In a study of American football players, 85% had suffered headache during play—21% during their most recent match. However, the majority of these headaches were related to trauma (14). A small study of Italian soccer players found a prevalence of 3.6% of reported headache during a season, all of which fulfilled the International Classification of Headache Disorders, second edition (ICHD-2) criteria for tension-type headache (TTH). No attacks occurred during competition (15). An estimation of the prevalence of primary exertional headache using International Headache Society (IHS) criteria in a large group of sports cyclists resulted in a rate of 26% (16).

Headache classification in sport

A previous study characterized sports headache as 'effort migraine' (9%), 'trauma-triggered migraine' (6%), 'exertional headache' (60%), 'post-traumatic headache' (22%) and miscellaneous (3%) (17). The IHS classifies three types of primary headaches that are relevant in this context—primary cough headache, primary exercise headache,

Box 55.1 International Headache Society primary headache relevant to headache in sport

Primary cough headache: headache precipitated by coughing or straining in the absence of any intracranial disorder

Diagnostic criteria:

A Either of the following:
- **1** A single headache episode fulfilling criteria B–D
- **2** At least two headache episodes fulfilling criterion B and either of criteria C and D.

B Brought on by and occurring only in association with coughing, straining, and/or other Valsalva manoeuvre.
C Sudden onset.
D Sudden onset, lasting from 1 second and 2 hours.
E Not fulfilling ICHD-3 criteria for any other headache disorder.
F Not better accounted for by another ICHD-3 diagnosis.

Primary exercise headache: headache precipitated by any form of exercise

Diagnostic criteria:

A At least two headache episodes fulfilling criteria B and C.
C Brought on by and occurring only during or after strenuous physical exercise.
B Lasting < 48 hours.
D Not better accounted for by another ICHD-3 diagnosis.

Primary headache associated with sexual activity

Headache precipitated by sexual activity, usually starting as a dull bilateral ache as sexual excitement increases and suddenly becoming intense at orgasm, in the absence of any intracranial disorder. Pre-orgasmic and orgasmic forms are recognized.

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and primary headache related to sexual activity (see Box 55.1 and also Chapters 24 and 25), and in contact sports head trauma itself may be an important consideration. These forms share similar clinical characteristics and may share similar pathophysiological mechanisms.

From a practical perspective, these classifications can be somewhat cumbersome in specific settings such as sports. Four categories of sport-related headache are defined that provide a pragmatic organization for practitioners (18):

1. A recognized primary headache syndrome (migraine, TTH, cluster headache) coincidental to sporting activity.
2. A recognized primary headache syndrome (migraine, TTH) induced by sporting activity.
3. Headache arising from mechanisms that occur during exertion.
   (a) Headache likely to be related to changes in cardiovascular parameters (increase in cardiac output and raised venous pressure; primary exercise headache).
   (b) Headache related to trauma.
   (c) Headache arising from structures in the neck.
4. Headache arising from mechanisms that are specific to an individual sport.

A recognized primary headache syndrome (migraine, tension-type headache, cluster headache) coincidental to sporting activity

Tension-type headache

TTH is the most common headache in the population (19). The headache is dull, occipital, and bilateral. However, it is usually improved by exercise, alleviated by simple analgesia, and unlikely to be a problem in sport.

Migraine

The overall lifetime incidence of migraine is 16%, while it is 43% in females (20). Although regular exercise can help reduce the frequency, intensity, and duration of migraine attacks (21), it is likely to be the most common coincidental primary headache during sport.

For the acute attack triptans, serotonin 5-hydroxytryptamine $(5\text{-HT})_{1B/1D}$ receptor agonists are the mainstay of treatment of disabling migraine. The experience of administration during sport, as systematically reported, limited to one small study of 38 attacks in Australian professional footballers using intranasal sumatriptan (22). There was a good response, with no major side effects and minor side effects being reported in > 70% of cases.

Apart from the potential impact of triptans on performance, particularly from a cognitive perspective, there are theoretical concerns regarding the potential for coronary vasoconstriction (23). For the amateur sportsman, a non-steroidal anti-inflammatory drug, with or without a prokinetic or antiemetic, would be a simple, generally safe, first choice. If triptans are necessary during sport in amateurs or in elite sportspeople, underlying cardiac pathology, in particular ischaemic heart disease and cardiomyopathy, should be excluded with an exercise electrocardiogram (ECG) and echocardiogram. Any of the first-line triptans, such as sumatriptan, almotriptan, eletriptan, rizatriptan, or zolmitriptan, represent reasonable initial choices. Triptan nasal sprays have the theoretical advantage of faster action and, to some extent, are able to bypass gastrointestinal absorption limitations. Triptan formulations that are rapidly dissolved are not faster acting but may be more convenient in the sporting context. Lack of or poor response to a triptan is not a class effect, and in this case an alternative from the class should be tried.

Beta blockers are a first choice in the preventive treatment of migraine in routine practice. Propranolol 20 mg twice daily increasing to 40–80 mg twice daily is commonly used, while atenolol is convenient, cheap, and may work just as well, starting with 25 mg daily and increasing at weekly intervals by 25 mg until effective, side effects, or a maximum dose of 100 mg daily is obtained. The use of beta blockers in many sports has obvious implications for limitation of performance and are banned in many professional sports. Topiramate, sodium valproate, candesartan, or pizotifen are possible alternative choices with appropriate monitoring for potential side effects.

Cluster headache

Cluster headache has a very high impact but is rare, affecting 0.1% of the general population. The cluster attack is predominantly

unilateral, periorbital, excruciatingly painful, and occurs in short bursts over a 'cluster period', associated with periorbital or nasal autonomic features. Ninety per cent of attacks occur daily for 6–8 weeks, typically once or twice a year with spontaneous resolution. Sporting activity will be unlikely during the cluster period.

Short-term oral corticosteroids and oxygen will be contraindicated for the elite athlete (the latter as it would give unfair advantage to aerobic performance). Triptans, either intranasal sumatriptan or zolmitriptan, or subcutaneous sumatriptan are effective. Cardiovascular concerns are the same as those outlined for the treatment of migraine. For prolonged bouts of episodic or for chronic cluster headache, verapamil is the preventive agent of choice but may cause cardiac conduction delays and 6-monthly ECGs should be undertaken. It is best avoided in elite athletes where lithium 600–1200 mg daily or topiramate 50 mg twice daily can be used. Greater occipital nerve injection may be a useful intervention in episodic cluster headache (24), but, again, corticosteroids will be contraindicated for the elite athlete.

A recognized primary headache syndrome (migraine, tension-type headache) induced by sporting activity

Over 20% of migraineurs experience migraine precipitated by physical activity (25). It has been suggested that exercise-induced migraine can be prevented by aerobic warm-up prior to activity (26), but the evidence base is poor. Cross-sectional studies have suggested that TTH does not restrict activities significantly (27).

As with all treatments in this area, there are no randomized trials and studies are invariably too small to be definitive. A reasonable approach would be to use indomethacin 25–50mg or naproxen 500–1000 mg 1 hour before the onset of exertion. If this is not successful, then indomethacin 25–50 mg three times daily or naproxen 500 mg twice daily over the 24-hour period prior to exertion can be useful. If the elite athlete has consistent problems, then a triptan administered 30–60 minutes before activity with the provisos mentioned could be tried, although the experience with triptans used in this way is variable, and evidence from menstrual migraine suggests frovatriptan 2.5 mg may be the best choice (28). If an elite athlete has consistent problems with sports-induced migraine it may be best to start a preventive, as outlined earlier. There is no evidence that cluster headache is induced by activity.

Headache arising from mechanisms that occur during exertion

The physiological processes that occur during sport can induce headache. If no underlying structural cause can be identified these headaches are termed primary, even though pain-inducing mechanisms may be inferred. If there is a structural abnormality, then the headache is termed secondary.

Headache related to changes in cardiovascular parameters

Headache associated with increased cardiac output

The formal IHS criteria classifies a 'primary exercise headache' as a pulsating headache lasting from 5 minutes to 48 hours for which no underlying cause can be identified and brought on by and occurring only during or after physical exertion. The headache is often described as migrainous in character, exacerbates in hot weather and at altitude, and typically occurs during the period of maximum exertion, although it can also be experienced during warm-up. It can be difficult in practice to dissect primary exertional headache from exertion-triggered migraine; migrainous features to the headache suggest using the approaches outlined earlier for exertionally triggered migraine.

Although mechanisms are unknown, arterial or venous distension may be implicated. Retrograde venous flow due to internal jugular vein incompetence has been suggested as one possibility (29).

Although studies are small, estimates of a secondary cause range between 10% and 23% (30,31). Risk factors for secondary headaches are age, late onset of headache during activity, and lack of responsiveness to indomethacin. All exercise-induced headaches should be investigated with a magnetic resonance imaging (MRI) of the brain, blood pressure and ECG, and blood screening for renal and liver function, haematology, thyroid disease and diabetes. Urinary catecholamines should be considered. Arnold-Chiari malformations, a structural abnormality in which the lower part of the cerebellum protrudes through the foramen magnum into the spinal subarachnoid space, and neoplasms are the most common secondary pathology. Subarachnoid haemorrhage and arterial dissection are the most common cause of acute presentations. Rarely, headache can be a direct and isolated symptom of cardiac ischaemia ('cardiac cephalalgia', see also Chapter 28), but the mechanism is unknown (32,33).

Having excluded a secondary cause, the treatment of primary exercise-induced headache is anecdotal. Gradual warm-up exercise programmes have been advocated (26), but for short-term prevention, indomethacin is the treatment of choice (34). For more frequent occurrence, a beta blocker is most often recommended, providing there is no contraindication for the elite athlete. There is little experience with other agents, but the preventive migraine agents described earlier can be tried.

Headaches due to raised venous pressure

This headache is more common in sports such as weight lifting and presumably caused by distension of the cerebral venous system. Intracranial hypotension is a rarer possibility but has been described (35).

As the small number of studies conflate this type of headache with exertional headache, and, indeed, in some types of exertion this may be the mechanism, the prevalence is unknown. An important secondary cause is an Arnold-Chiari malformation, which must be excluded with neuroimaging with MRI. However, the indication for surgical treatment within the sporting context is contested, and it should be remembered in adolescents that minor malformations may resolve with time.

When no underlying cause can be identified this is classified by the IHS as 'primary cough headache', although the previously used term 'Valsalva manoeuvre headache' is more accurate. Indomethacin is claimed to be effective, although a positive response has been reported in some cases where there is an underlying cause.

Headache related to trauma

Headache is the most common symptom of a concussive injury and post-traumatic headache (PTH) accounts for 4% of all symptomatic

headaches (see also Chapter 35). Post-traumatic headache (PTH)—both acute and chronic—is the most common sports-related headache with an estimate incidence in the USA of up to 3.8 million a year (36).

Head injury involves shearing due to linear acceleration/deceleration or rotational forces. The degree of injury does not always correlate with headache symptoms and the mechanisms that generate pain are poorly understood (37). Headache may be due to direct stress acting on dural structures or secondary mechanisms due to bleeding or axonal damage.

The headache can occur immediately or within the first week following an injury. In many cases athletes may not be aware of the initial head injury. Later-onset headaches have been described, but their causality is contested. There is an inverse relationship between the development of PTH and the severity of the injury (38), but most cases resolve in the first 3 months following an injury.

As published studies are not case controlled, the exact relationship between headache and trauma is not clear (39). A variety of pain patterns may develop, some of which resemble primary headache disorders. TTH is the most common. In some cases migraine, known as 'footballers' migraine' can be triggered by mild head trauma (40,41). More rarely, a cluster headache-like syndrome has been described (42). Alternatively, a pre-existing primary headache can be made worse in close temporal relationship to trauma, making them more refractory to treatment (43).

Chronic PTH is a headache that persists for 3 months after head trauma in the absence of a demonstrable traumatic brain lesion. It may be due to maladaptive central sensitisation, and is invariably associated with a number of other symptoms such as dizziness, difficulties in concentration, and insomnia. Recently, a relationship was found between different alleles of the apolipoprotein E gene and headache following sports-related concussion (44). The e4 allele gave an increased risk of developing headache. The relationship between the severity of the injury and severity of the post-traumatic syndrome is not always direct. The phenotype of the headache is very often that of chronic migraine, as documented in the systematic description of these issues in a study of US military (45).

There is no evidence base for the treatment of PTH (46,47). The first line of treatment is symptomatic and medication overuse headache is always a cause for concern if analgesics are taken on more than 3 days in each week over the longer term. Amitriptyline can be effective (48). From a practical perspective, start with 10 mg and increase by 10 mg each night every 4–10 days until side effects are problematic or a maximum dose of 1–1.5 mg per kg body weight is reached.

Propranolol and valproate have also been suggested as treatment (40). Other options are trigger point injections, occipital nerve blocks, and botulinum toxin type A. However, a number of patients will remain disabled for some years following the insult and provide a clinical challenge. Developing secondary causes such as intracerebral or subdural haemorrhage, and, more rarely, vertebral artery dissection should not be overlooked.

Headache arising from structures in the neck

Trauma to the neck can induce or exacerbate a cervical lesion with subsequent referred pain to the head via the upper cervical nerves (see also Chapter 36). For a cervicogenic headache to be diagnosed, the IHS criteria require:

- evidence of a disorder within the cervical spine or soft tissues of the neck as a valid cause of headache;
- clinical signs that implicate a source of pain in the neck or the abolition of headache following a diagnostic blockade;
- pain resolving within 3 months after successful treatment of the causes of lesion or disorder.

From a practical perspective, if the patient is able to demonstrate full movement of the neck with no local tenderness, cervicogenic headache can be excluded.

Headache arising from mechanisms that are individual to a specific sport

A number of headaches unique to a sport have been described that have a specific aetiology. For example, headache in spinning figure skaters is thought to be due to a centrifugal effect causing intracranial ischaemia (49), which is a claim without very considerable support given the fact that headache is certainly not an invariable rule in stroke. External compression headache is seen in swimmers as a result of mask pressure (50). High-altitude headache is recognized as an accompaniment of acute mountain sickness and may be associated with vascular phenomena (51). Diving headache occurs as a result of carbon dioxide intoxication (see also Chapter 56) (52).

Headache medication in elite sportspeople

There is the possibility that performance-enhancing drugs can induce headaches and this should always be considered.

The Global Drug Reference Online (www.globaldro.com) provides athletes and support personnel with information about the prohibited status of specific substances based on the current World Anti-Doping Agency (WADA) Prohibited List and is relevant for those wishing to use prescribed and non-prescribed medication for their headache. If the medication an athlete is required to take to treat an illness or condition happens to fall under the Prohibited List, a Therapeutic Use Exemption may give that athlete the authorization to take the needed medicine. This will depend on the sport and country where it takes place. Further details are available from WADA (www.wada-ama.org).

Conclusion

There are a number of problems with the study of headache in sport: the evidence base is very limited and studies are retrospective, leading to recall bias; formal diagnostic criteria are rarely used; the pathogenesis of the majority of headaches is poorly understood; and different types of activity may lead to different pathophysiological mechanisms. The impact of headache on sport is also likely to reflect the perspective of headaches sufferers in the community, i.e. stigmatized, largely unrecognized, and inadequately managed, with the needs of many sufferers unmet. For the research community, a

useful first step would be to quantify formally the prevalence of this problem.

Further research is also needed to define more accurately the extent of the problem and options for management. An important first step is an awareness of the problem by the general practitioner, sports physician, and those involved in sport, and the encouragement of activity in the population at all levels.

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56

Headache attributed to airplane travel

Federico Mainardi and Giorgio Zanchin

Introduction

Headache attributed to airplane travel, also named 'airplane headache' (AH), is a recently described clinical entity characterized by the sudden onset of a severe head pain, which appears exclusively in relation to airplane flights, mainly during the landing phase. Secondary causes, such as upper respiratory tract infections or acute sinusitis, must be ruled out. Although its pathophysiology is not completely understood, a causative role is attributed to an imbalance of the intrasinus pressure, consequent to a change of external air pressure not paralleled by adequate compensation inside the cranial sinuses. In the International Classification of Headache Disorders, second edition (ICHD-2) (1), AH is not mentioned. On the basis of an extended investigation, we proposed AH diagnostic criteria, which have been introduced for the first time in ICHD, third edition, beta version (ICHD-3B) (2), and confirmed in the recently published final version (3). Its formal recognition will favour further studies aimed at improving its knowledge and implementing preventative measures.

Historical outline

The very first description of a change of atmospheric pressure as a possible cause of headache may be identified in a report of 1783: Jacques Charles, a French engineer who, along with the Robert brothers, had built an air balloon, complained of an intense pain during a rapid ascent; after this, he gave up flying (4). More than a century later, on December 1903, the era of aviation began, when the Wright brothers performed the first flight on their own projected air machine. Since then, several people have reported their experience of unbearable pain related to flight. Among them, Amelia Earhart (1897–1937), a pioneer of American women aviators, suffered from episodes of sinusitis, which affected her flying activities (5). This disturbance received special attention during World War II, when fighter pilots, exposed to rapid altitude changes, had to face an increased risk of its occurrence (6). Several direct experiences have been recorded by the pilots themselves. In a self-written biography, the Japanese Zero fighter pilot Saburo Sakai reported his own experience, which occurred in 1940 when he was unable to continue a landing approach due to the sudden onset of an excruciating pain in half of his head. The pain reappeared on each attempt he made, and the Valsalva manoeuvre failed to give relief (7). A pilot, Lieutenant Moore, a member of the crew that operated the first mission to Saarbrucken, was relieved of his flying status because of his 'chronic sinusitis' problems, although the X-ray evaluation was considered normal by the flight surgeon (8).

The term aerosinusitis was introduced in 1942 by Paul Campbell (9). In 1945, he proposed a classification of this condition based upon the description of five cases, inclusive of their histopathology (10). He proposed the recognition of two different forms of aerosinusitis: the non-obstructive one, in which the pain is sustained by an infection in the nasal cavity, which causes a flow of mucus into the sinus; and the obstructive form, where polyps or a swollen, inflamed mucosa partially obstructs the sinus ostia, creating a sort of valve mechanism. Campbell stressed the importance of the cabin pressurization as an adjunctive precipitating factor.

The advancement of the techniques to obtain the cabin pressurization, which even nowadays is purposely partial, has reduced but not completely removed the risk of sinus barotrauma.

A complete overview on the history of AH was recently published (11).

Background

The first case of AH was reported in 2004 (12), and a case series including six patients was published 2 years later (13). Up to 2012, 39 well-documented cases had been published (12–24). Owing to the paucity of cases of such a peculiar headache, AH was deemed to be relatively rare. However, a Danish survey found that 8.3% of 254 patients responding to a questionnaire reported AH (25). In a multicentric Italian survey, AH was found up to 4% of an outpatient population referred to the Headache Centre (26).

After the publication in 2007 of a paper in which the first Italian case of AH was described (14), and provisional diagnostic criteria based on the very typical features shared with the previously published cases proposed (12,13), patients who had experienced this pain contacted us. They agreed to fill in an anonymous, structured questionnaire regarding their headache, aimed at obtaining all the relevant information that could clinically characterize this peculiar disorder. The results, based on a large case series, were first published

Box 56.1 Headache attributed to airplane travel: ICHD-3 criteria

A At least two episodes of headache fulfilling criterion C.
B The patient is travelling by airplane.
C Evidence of causation demonstrated by at least two of the following:
  1 Headache has developed during the airplane flight
  2 Either or both of the following:
    (a) Headache has worsened in temporal relation to ascent following take-off and/or descent prior to landing of the airplane
    (b) Headache has spontaneously improved within 30 minutes after the ascent or descent of the airplane is completed
  3. Headache is severe, with at least two of the following three characteristics:
    (a) Unilateral location
    (b) Orbitofrontal location
    (c) Jabbing or stabbing quality.
D Not better accounted for by another ICHD-3 diagnosis.

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in 2012–2013 (27,28), and expanded and updated in 2018 (29). In these papers, we proposed provisional diagnostic criteria slightly modified in comparison to those that, suggested in 2007, had been accepted in the description of the cases published since then (16–19,21,22,30). Different diagnostic criteria were also suggested (23). The diagnostic criteria we proposed in 2012 (27) have been accepted in their more relevant aspects in the ICHD-3 (Box 56.1), where AH appears for the first time in Chapter 10 among other forms of headache attributed to disorder of homeostasis (coded 10.1.2).

Clinical features

AH should be diagnosed only after other possible disorders affecting the sinuses, in particular acute and chronic sinusitis, have been ruled out (31–35), mainly with neuroimaging and/or an otorhinolaryngology visit when appropriate. Indeed, the features of AH appear to be similar to those that can affect aviators or air passengers who carry an upper respiratory infection during the flight. This well-known condition is mainly due to sinus barotrauma, which occurs when intrasinus and intranasal pressure equilibration is impaired by the relative obstruction of the sinus ostia.

In our recent study (29), we analysed the clinical features of 200 subjects who suffered recurrent headache attacks during airplane travel. Clear and well-characterized symptoms were reported, stressing the highly stereotyped features of the pain (12–14,23).

The initial observation (14), showing a male preponderance and an early age at onset of AH, was confirmed in our case series, as 60% were male and the patients' mean age was 37.3 years. No patients had symptoms and/or signs related to inflammatory sinus disorders when they experienced the AH attacks, including those (about 20%) with a past history of sinusitis. This is an important diagnostic prerequisite that allows differentiation of AH from the similar pain that can occur in people who fly when they are affected by sinus inflammation. A positive history for allergy is reported by about one-third of patients. Almost a fifth of subjects (18%) are smokers, with no differences between males and females. Although an AH attack can occur during each phase of the flight, in the large preponderance of cases (92%) attacks occur during landing. AH only occasionally starts during take-off or cruising, but in most of these cases the attacks also occur during landing. In only six patients was AH not associated with landing (exclusively during take-off, n = 3; exclusively during cruising, n = 3) (Table 56.1). There is no evidence of a role of different geographical locations of the airports. The airport altitude appears also not to be a potential aggravating or triggering factor.

Table 56.1 Headache onset in respect to flight timing.

Flight timing	n	%
Only during landing	184	92.0
Only during take-off	3	1.5
Landing > take-off	5	2.5
Landing = take-off	2	1.0
Landing < take-off	1	0.5
During cruising	3	1.5
During cruising, subsequently only during landing	1	0.5
During both cruising and landing	1	0.5
Total	**200**	**100**

In almost 85% of cases the onset is not concomitant with the first flight and, noteworthy, in less than 19% of patients an attack occurs during each flight. Only 33% suffer AH in more than 50% of their flights, whereas in 24% attacks are occasional.

The pain intensity is reported as severe by all patients (Table 56.2), the mean intensity scoring being 9.1/10 on a visual severity scale, where 0 represents no pain at all and 10 represents pain as severe as possible. More specifically, it is defined as being extremely severe/unbearable by more than 90%.

In the large majority of cases (88%) it is strictly unilateral, involving the fronto-orbital (80%) or frontotemporal (9%) regions. In about 12% the headache is bilateral, diffuse, or on the vertex. Among patients with unilateral headache, in the vast majority the pain constantly recurs on the same side throughout the different flights; only in about 11% is there a side shift in different flights. The quality of the headache is most frequently defined as stabbing (about 65%). Other descriptions were pulsating, jabbing, pressing, and electric shock-like (Table 56.2).

The pain starts suddenly, reaching its peak in a few seconds. In more than 95% of cases it subsides spontaneously within 30 minutes, at the end of the flight phase in which it occurs, usually landing. A postictal, much milder headache, following the acute phase of AH is reported in up to 28% of the cases; it persists for several hours (up to 24 and 48 hours, respectively, in 4% and 22%) in half of these subjects, while it disappears within 1 hour in one-quarter of the patients (Table 56.2).

Accompanying symptoms were referred up to 30% of the subjects, the most common being restlessness (n = 40; 20.0%), followed by unilateral tearing (n = 28), conjunctival injection (n = 4), photophobia (n = 3), phonophobia (n = 2), and nausea (n = 2). No patient complained of vomiting, smell or perfume intolerance, ptosis, rhinorrhoea, nasal stuffiness, forehead sweating, miosis, or aura. Anxiety was constantly present during the attacks (Table 56.3).

Table 56.2 Clinical features of headache attributed to airplane travel.

	n	%
Duration	199	
< 10 min	12	6.0
>10 and ≤ 30 min	179	89.9
> 30 min	8	4.0
Postictal mild intensity	55	27.6
< 1 h	14	25.5
> 1 < 24	29	52.7
> 240	12	21.8
Severe intensity	200	100
Side	199	
Unilateral	176	88.4
Without side shift	122	69.3
With side shift	44	25.0
Single attack	10	5.7
Bilateral/diffuse	22	12.5
Location	198	
Fronto-orbital	158	79.8
Frontotemporal	18	9.1
Frontoparietal	10	5.0
Others	12	6.1
Quality	200	
Jabbing or stabbing	154	77.0
Pressing	18	9.0
Electric shock	15	7.5
Pulsating	13	6.5

Table 56.3 Emotional impact of airplane headache on patients.

	n	%
Yes	**160**	**80.0**
Continue to fly with anxiety and/or worry	122	61.0
Fly only if strictly necessary	27	13.5
Give up flying	10	5.0
Only air travel < 2 h	1	0.5
No	**40**	**20.0**

Interestingly, an emotional impact of AH attacks is reported in 80% of cases. Approaching the flight with anxiety was the most frequent attitude stressed by the patients, even after receiving reassurance about the benign nature of the pain. Concerned with the fear of suffering a further attack, they continue to fly with worry, whereas a minority decides to fly only if strictly necessary or gives up flying (Table 56.3). Therefore, apart from the suffering due to the pain severity, the attacks negatively influence the attitude to flying.

A specific section of the questionnaire focused on the possible co-existence of a primary headache according to the ICHD classification (2). The symptoms reported are consistent with a concurrent primary headache in more than a half of the patients, mainly tension-type headache and migraine without aura. No patients reported symptoms suggestive of cluster headache. These findings on one side are in keeping with the hypothesis of a possible facilitating role on AH of a pre-existing periodical activation of headache pain pathways; on the other, they would rule out a possible relationship between AH and cluster headache, despite some clinical features being quite similar. Of our AH patients, 16% suffer headache also during the rapid descent of a mountain by car. They complain of AH attacks in more than 50% of their flights. These patients (nine men, 11 women, aged 37 ± 11 years) report the occasional occurrence of stabbing, severe, unilateral headache in the fronto-temporal region, which begins shortly after the fast descent by car from an average altitude of 1920 (range 1800–2000) metres, the maximum peak of intensity developing in a few minutes. In all of them the pain disappears within 30 minutes after the end of their rapid decline. As a whole, they describe this headache as having the same features as AH. No accompanying symptoms or concomitant airway disturbances are reported. Neurological evaluation, brain magnetic resonance imaging (MRI), magnetic resonance angiography (MRA) and cranial computed tomography (CT) scan for sinusitis are normal. The co-existence of AH with headache attacks sharing the same features during a rapid descend by car from a mountain height is reported in literature in just a few cases (18). Curiously, after knowing the results of our studies on the subject, a patient, who never travelled by airplane, contacted us to refer her AH-like attacks when rapidly descending from a mountain and declared that the fear of experiencing similar episodes during airplane journeys induced her to completely avoid flying (36). However, according to our data, assuming that around 10% of patients with AH also suffer from headache caused by the rapid descent of a mountain in a car, its occurrence should not be so rare.

Furthermore, 21 patients among the 46 that reported diving (14 men and seven women, aged 35 ± 10 years) experience the occurrence of stabbing, severe, unilateral headache attacks in the frontotemporal region during free or scuba diving. All of them complained of AH in more than 50% of flights. In eight cases the pain occurred in > 30% of the dives. One patient complained of the headache sporadically, whereas the remaining patients did not specify the frequency of headache. Headache is described as having the same features of AH. Fourteen patients were free-divers, attaining a maximum depth of 5–8 metres; seven patients were scuba-divers, reaching an average depth of approximately 20 metres. The pain starts shortly after the ascent, building up to peak intensity in a few minutes, and disappears spontaneously within 30 minutes. No accompanying symptoms or concomitant airway disturbances are reported. Neurological evaluation, brain MRI, MRA, and cranial CT scan for sinusitis are normal.

In the ICHD-3 (3), clinical entities named 'High altitude headache (10.1.1)' and 'Diving headache (10.1.3)' are classified. However, the first is related to hypoxia, the second to hypercapnia. Clearly, the conditions we just described, which could take the name of 'Headache attributed to rapid descent from altitude (mountain descent headache)' and of 'Headache attributed to rapid ascent from diving (diving ascent headache)', recognize different pathophysiological

mechanisms from 10.1.1 and 10.1.3, as we are going to discuss, and deserve further studies.

Pathophysiology

The pathophysiology of AH remains speculative. The co-existence of headache attacks, sharing peculiar features, triggered by these different situations—landing by airplane, ascent after diving, and descent from high altitude by car—strengthens the hypothesis of a possibly common pathophysiological mechanism, i.e. of the causative role of an imbalance of the intrasinus pressure, consequent to a change of external air pressure not paralleled by an adequate compensation inside the cranial sinuses. As already stated, the exclusion of other possible conditions underlying AH is mandatory, given the existence of similar clinical pictures attributable to paranasal sinus disorders. Indeed, the occurrence of an extremely severe pain during take-off or landing in patients affected by sinus infections has been known for a long time, particularly in aerospace medicine (37): the Aerospace Medical Association guidelines consider middle ear and sinus infections as contraindications to flight. In the same guidelines the use of nasal oxymetazoline is suggested to treat pain occurring during flying in such condition (38).

However, an underlying sinus inflammatory disorders is excluded in our patients with AH: the sudden onset and the quick resolution of AH pain without previous or subsequent signs/symptoms attributable to sinus disorders, and the absence of abnormal findings on radiological/physical evaluations, allow us to rule out this possibility.

The pressure changes within the paranasal sinuses in relation to the modification of external pressure follow Boyle's law, which maintains that, at a given temperature, the volume of gas varies inversely with the pressure exerted on it. Accordingly, during airplane flights, on ascent the air in the sinuses will expand, whereas it will contract during descent. In normal conditions, the sinuses drain into nasal cavity through small ostia, which permit mucus clearance and ventilation that equilibrate pressure; the external versus intrasinus pressure differential is zero, as pressure changes are freely compensated through patent sinus ostia. However, if patency is marginal, changes of cabin pressure cannot be equilibrated in a timely fashion within the sinus. In this circumstance, during take-off the decrease of barometric pressure is paralleled by an expansion of intrasinus gas volume, affecting the walls of the sinus and producing pain. During landing the situation is reversed, in relation to the rapid increase of barometric pressure; the pressure in the obstructed sinus remains relatively low, resulting in a vacuum effect, sometimes referred to in the literature as 'the squeeze', which may be stressful to the sinus mucosal lining. The consequence, called sinus barotrauma, is an acute, in most cases short-lasting, inflammation of the sinuses. The pain—severe and sharp—is the predominant symptom and is localized in the frontal area (31–35), probably because of the main involvement of a frontal sinus.

However, the physiological intrasinus changes due to external pressure modifications during airplane travel cannot explain why some individuals suffer from AH and other do not. On equal terms of external conditions, it could be speculated that all the passengers during a particular flight should experience AH. Nor can individual malformations of sinus ostia completely elucidate AH physiopathology, as in an individual patient AH can start after several normal flight experiences and does not recur consistently in following flights: in our series, only about 18% of patients reported the constant occurrence of AH during each flight. Therefore, the most likely AH pathophysiology seems to be related to an interacting variety of multimodal contributing factors: anatomical factors, such as acquired or congenital abnormalities of sinus outlet; environmental factors (cabin pressure, aircraft speed, angle of ascent/descent, maximum altitude); concurrent factors that act by reducing the sinus ventilation, such as a temporary mucosal oedema, possibly worsened, in predisposed individuals, by the above reported alterations. A patient suffering from thunderclap headache during airplane descent due to a reversible cerebral vasoconstriction syndrome (see also Chapter 49) was described, showing that mechanisms other than pressure changes in the nasal sinuses may also be considered (39,40).

Airplane headache management

Non pharmacological treatment

In previous research, we found that about 65% of the patients suffering from the main primary headaches migraine without aura and with aura, tension-type headache, and cluster headache, perform spontaneous manoeuvres to decrease the pain intensity (41). A slightly lower percentage (51%) of patients with AH spontaneously performs one or more manoeuvres with the same purpose, represented mainly by pressure on the pain area and Valsalva manoeuvre. The efficacy of these manoeuvres is scant or temporary, apart for the Valsalva manoeuvre, with which a pain reduction of at least 50% is reported only by 10% of patients. Only one patient experienced a persistent and complete remission of the pain after Valsalva manoeuvre.

Pharmacological treatment

Despite the severity of the pain, < 40% of patients in our series resort to a pharmacological treatment, most commonly simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs) and nasal decongestants. These drugs are not taken after the onset of pain, but used as prophylactic therapy before the expected triggering phase of the flight (29). The subjects took the medication about 30 minutes before the expected attack, i.e. before landing in the vast majority of cases. A therapeutic efficacy of at least 50% was reported by more than half of the patients (55%), being completely effective in preventing the occurrence of the attacks in about 32%; among them, a satisfactory response to sumatriptan was reported by the only patient who used it. In 19% no benefit was reported. Based on the available data, it is not yet possible to draw definitive therapeutic indications. However, the drugs that were demonstrated to be of benefit—oral NSAIDs and nasal decongestants—are more likely to provide a significant efficacy when taken about 30–60 minutes before the expected triggering phase of the flight (29). A complete response to triptans has been reported in five cases (20). In addition, we observed the long-lasting preventive action of frovatriptan in a young migrainous woman, who suffered from AH in 75% of her flights (42). The efficacy of triptans is hypothesized to be related to the counteractivation of the trigeminovascular system consequent to the stimulation of paranasal mucosa during AH attacks (35). Should the efficacy of triptans be confirmed in

future studies, these drugs could be the first-choice medication when NSAIDs and decongestants are ineffective, poorly tolerated, or contraindicated.

Conclusion

AH does not appear to be rare and it is expected to become a more and more frequently reported and relevant condition: indeed, airplane travel is a largely shared experience, with more than 3.3 billion seats offered annually on commercial flights, with an occupancy of 70%, and it has been predicted that in the coming two decades, the number of passengers will increase exponentially (43). Very typical and not to be confused with other forms of headache related to flight (37,43), AH is characterized by severe pain, which exerts a deep impact on patients, given the suffering and the anxiety associated with a negative attitude towards possible future flights. Preliminary data would suggest that simple analgesics, NSAIDs, nasal decongestants, and probably triptans could be effective in the majority of patients when taken prophylactically shortly before the expected AH attack.

The observation of headaches showing similar clinical features, but triggered by different situations, such as landing by airplane (AH), fast descent from altitude (mountain descent headache), or diving ascent (diving ascent headache), strengthens the hypothesis of a possibly common pathophysiological mechanism, i.e. the inability to equilibrate timely the intrasinus/external pressures, which is shared by these conditions. Therefore, we propose to classify them together in the next ICHD within Chapter 10, 'Headache attributed to disorders of homoeostasis', with a unique headline: 'Headache attributed to imbalance between intrasinusal and external pressure'.

The growing attention among researchers (23,44,49), and its recent, formal recognition as a new form of headache in ICHD-3 (**Box 56.1**), should lead to further studies, improving our knowledge of AH pathophysiology and implementing the efficacy of therapeutic measures, as recommended in an authoritative editorial (49).

In the interest of passengers, airlines should insert a notice about the possible occurrence of AH in the cabin leaflet, reporting the measures to take in order to have a healthy journey.

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57

Headache and sleep

Stefan Evers and Rigmor Jensen

Introduction

Headache and sleep obviously show several clinical links, for instance by being both paroxysmal and carefully classified. Even in antiquity good sleep was suggested to be a cure for headache and bad sleep was said to be a trigger for headache. More than 88 sleep disorders are differentiated in the International Classification of Sleep Disorders (ICSD) (1). About 15% of all adults suffer from sleep disorders requiring treatment (2), and about 75% of all headache patients report concomitant sleep disorders (3). Chronic insomnia, for example, can induce unspecific headache, which is different from tension-type headache (TTH) (4). More frequently, however, sleep disturbances are caused by headache disorders. Sometimes sleep and headache show an undetermined link, such as in cluster headache. In addition, drugs used in headache treatment can cause sleep disturbances and vice versa. All these aspects are reviewed in this chapter.

For hypnic headache as a model of the interrelation between headache and sleep, see Chapter 26.

Anatomy and physiology of headache and sleep

The basis for all functional and pathophysiological considerations concerning the link between headache and sleep is the anatomy of the midbrain. A variety of such brain structures share functions, both in sleep biology and in pain processing. These structures together with the specific structures for pain and sleep processing are shown in Table 57.1, which is adapted to another review (5).

Sleep anatomy

One has to differentiate between those structures involved in arousal and those involved in inducing and maintaining sleep. The most important arousal-inducing structures are cholinergic and monoaminergic nuclei of the brainstem. Two different arousal streams act separately but in coordination (6). Firstly, a stream projecting from the pedunculopontine nucleus and the laterodorsal tegmentum to the thalamus is important for suppressing sleep-initiating activity in the thalamus. Secondly, a stream projects more diffusely from the midbrain to the hypothalamus (e.g. from the locus coeruleus, from the nucleus raphe, from the periaqueductal gray (PAG)). Different excitatory neurotransmitters are responsible for all these projections, which all converge in the lateral hypothalamus. This is important for the homoeostasis of orexin, a central molecule for sleep induction, which has also been related to pain processing (7).

Sleep itself is mainly induced by suppressing the activity of the nuclei listed in the previous paragraph by inhibitory transmitters such as γ-aminobutyric acid and galanin (8). The primary sleep-inducing molecule is adenosine, which accumulates during the day and activates the ventrolateral preoptic hypothalamus (9).

Another mechanism inducing sleep is the endogenous circadian sleep drive, which originates in the suprachiasmatic nucleus of the hypothalamus. This circadian sleep drive has an intrinsic activity rhythm of slightly more than 24 hours (10) and is further modulated by retinal inputs during the day and by melatonin production of the pineal gland during dawn and night.

The transition from wake to sleep and vice versa is nowadays interpreted as a flip-flop switch (11). This means that the brain prefers either state but not the state of transition. Also, the transition between rapid eye movement (REM) and non-REM (NREM) sleep most probably follows such a flip-flop mechanism. The anatomical basis for this transition can be found near the locus coeruleus, where neurons are localized that activate REM sleep, and in the ventrolateral PAG and lateral pontine tegmentum, where neurons with off-REM properties are localized. This latter region is of particular interest as its neurons contain orexin-2 receptors, which are activated by orexin from the lateral hypothalamic area. This area is active during wakefulness but inactive during REM sleep.

The neuroanatomical link between headache and sleep

After synapsing in the trigeminal nucleus caudalis (TNC), nociceptive fibres project to the ventral posteromedial thalamus by indirect or direct connections with the hypothalamus via specific neurons.

In addition to these efferents, there are also collaterals from the TNC to the solitary tract and the parabrachial nucleus. These structures are the main control centres for viscerosensation. Furthermore, processing of pain interacts via these collaterals with other vegetative functions such as sleep, arousal, sympathetic and parasympathetic functions (e.g. pupil function, secretory function), and neuroendocrinological functions. Vice versa, it is very likely that pain processing can be modulated via these circuits by vegetative/autonomic symptoms and reflex mechanisms. This means that

Table 57.1 Anatomical structures involved in both the biology of sleep and pain processing.

Brain structure	Sleep function	Pain function
Nucleus caudalis nervi trigemini	None	Trigeminal pain processing (for headache: mainly ophthalmic division)
Raphe nuclei (medialis)	REM sleep activation; arousal activation	Visceral and affective pain processing
Locus coeruleus	REM sleep activation	Visceral pain processing; endogenous antinociception
Periaqueductal gray (PAG)		
Raphe nuclei (dorsalis)	REM sleep activation	Visceral and affective pain processing
	Arousal activation	Endogenous antinociception
Ventrolateral PAG	REM sleep activation	Visceral pain processing
Hypothalamus		
Ventrolateral preoptic	Slow-wave activation	None
Nuclues suprachiasmaticus	REM sleep activation	None
Posterior	None	General pain processing[a]
Lateral	Activated by arousals	None
Thalamus		
Ventral posteromedial	None	Discriminative pain processing
Ventral and intralaminar	None	Visceral pain processing
Mediodorsal	None	Affective pain processing
Cortex		
Somatosensotory	None	Discriminative pain processing
Insula	None	Visceral pain processing
Limbic and gyrus cinguli	?	Affective pain processing

REM, rapid eye movement. [a]Functional imaging suggests a specific role in trigemino-autononnic cephalalgias.

changes of the autonomic homoeostasis (e.g. in sleep) can facilitate or inhibit pain processing.

A very important role in the complex interactions of pain and sleep is played by the antinociceptive system (i.e. by the descending pain control system). At the lower brainstem and pons level, different structures can be identified, which project to the dorsal horn and reduce pain activation on the spinal and TNC level (12). Another important antinociceptive structure is the PAG, which itself is not only involved in antinociception, but also in regulating autonomic functions such as blood pressure and heart rate. The ventrolateral part of the PAG is probably the most interesting anatomical region for the connectivity of headache and sleep. The ventrolateral PAG can cause REM sleep off when activated by orexin. Furthermore, orexin can stimulate neurons in the ventrolateral part of the PAG, which inhibit antinociceptive activity in the TNC (i.e. facilitate trigeminal nociception) (13).

The hypothalamus plays a crucial role in the nociception of the trigeminal system. For headache, this has been demonstrated in functional and structural brain imaging for migraine and the trigeminal autonomic cephalalgias (TACs). The most important part of the hypothalamus involved in nociception is its posterior part. It has, for instance, already been known for a long time that installation of opioids into this part can induce a profound analgesia (14), and neurostimulation of this area is helpful in TAC. The posterior hypothalamus and the neighbouring parts of the hypothalamus and its surroundings contain orexinergic neurons (15). These neurons are involved both in inhibition of analgesia and in sleep disorders such as narcolepsy (in particular, loss of these neurons can lead to sudden sleep onset).

As orexin is currently one focus of basic headache research, this shall be discussed in more detail. Orexin A and B are neuropeptides synthesized exclusively in the hypothalamus (16) and binding to two similar receptors. It has been suggested that orexins are involved in the transition from episodic to chronic migraine as they regulate a number of neuroendocrine and autonomic functions such as obesity and medication overuse, and other addictive behaviour (16). Furthermore, the orexinergic activity in the ventrolateral PAG can be blocked by antagonism of the 5-hydroxytryptamine $(5\text{-HT})_{1B/1D}$-receptor, and antagonism of the orexin-1 receptor delays the onset of triptan-induced inhibition (16). It can thus be concluded that triptans might influence the sleep–wake cycle and autonomic functions that are regulated by orexins.

With respect to the genetics of the orexin receptors, controversial results have been obtained. Some polymorphisms of the orexin-2 receptor have been linked to cluster headache in the majority of studies (17–19), but not in all (20) and not to treatment response in cluster headache (21). Studies of the same polymorphism in migraine did not reveal a significant association (22,23). Another gene involved in circadian rhythmicity, the *CLOCK* gene, could also not be linked to cluster headache (24).

The role of melatonin

Melatonin is a specific hormone that is synthesized from serotonin by the pineal gland. The production of melatonin is highly regulated by light, with high secretion during darkness and low secretion during light. In humans, the secretion of melatonin rises in the evening, peaks at midnight, and then slowly again decreases.

In some chronobiological headache disorders, changes of melatonin have been found. Cluster headache shows a decrease of both peak and median melatonin secretion. This is more pronounced during the cluster headache episode (25). To a smaller extent, a decrease of melatonin secretion has also been observed in migraine (26). This was, however, only significant for female migraine patients. Further, the secretion of melatonin in migraine patients is more sensitive to light than in controls (27).

A role of melatonin in headache is also supported by treatment trials, although the results are somewhat controversial and inconsistent. Episodic but not chronic cluster headache was reduced by melatonin in a small placebo-controlled trial (28); in a case series, chronic cluster headache was also alleviated by melatonin (29). However, another small placebo-controlled trial did not find any benefit from melatonin in cluster headache (30). For migraine, some positive open reports on the efficacy of melatonin exist (31), but, again, another placebo-controlled trial was negative (32). In conclusion, there is evidence for a role of melatonin in headache, in particular in chronobiological subtypes. However, the results of the rare

and small treatment trials also show that this hormone cannot be the major player in the induction of headache during sleep.

Impact of headache disorders on sleep and sleep architecture

In this section, the interrelation between primary headache disorders and sleep architecture will be explained. Sleep fragmentation (e.g. in cluster headache or paroxysmal hemicrania) can be caused by a common underlying pathogenetic mechanism or by the pain itself, or by the fear of a new attack during sleep (33–35). Therefore, a psychogenic origin of sleep disturbances in headache patients is often considered (36). An overview of sleep disturbances caused by headache disorders is given in Table 57.2.

Migraine

Migraine attacks often occur during sleep stages 3 and 4, but even more often during REM sleep (36–39). They can also occur during daytime sleep and by changes of sleep pattern at the weekend, during a holiday, or after stressful periods with extremely long sleep thereafter (38,40,41). In the nights before a migraine attack, decreased REM density and arousals were observed (42). Furthermore, it has been reported that vivid and frightful dreams can result in migraine attacks; this might indicate an influence of physiological and psychological stress-associated factors on the onset of migraine attacks (43,44). A significant proportion of migraine attacks is related to insomnia (45).

With falling into sleep, a relief of migraine symptoms is often reported, in particular in children who regularly report freedom from headache when they awake after a migraine attack (36,46,47). In migraine patients during the interval between two attacks, an increase of REM sleep duration and of REM sleep latency (48) and a decrease of deep sleep stages and lower sleep efficiency (49) could be shown; otherwise, there are no significant changes of the sleep profile. In the nights after a migraine attack, an increase in deep sleep stages compensates for the sleep disturbances during the attack (50). An increased pain threshold in the interval between attacks has been shown for those migraine patients with sleep deprivation (a common phenomenon in migraine) (51). Altogether, sleep disturbances in migraine result in increased daytime sleepiness and poor sleep quality, which has been shown in several cohort studies (52,53); in particular, patients with chronic migraine suffer from excessive daytime sleepiness (54,55).

The pathogenetic link between migraine attacks and sleep is still unclear. The frequent occurrence of migraine attacks during REM sleep points to a vulnerability during the transition from excitatory to inhibitory sleep stages (41). Furthermore, instability of platelet serotonin content has been reported in migraine patients during sleep stages 3 and 4, and during REM sleep (38). Serotonin is an important factor in the pathogenesis of sleep disturbances and of migraine (37,38).

Table 57.2 Alteration of sleep architecture in primary headache disorders.

Headache disorder	Sleep architecture
Hypnic headache	Fragmentation of sleep profile
Migraine	Increase of REM sleep in the interval, increase of deep sleep stages after an attack
Cluster headache	Fragmentation of sleep profile, increase of wake time, decrease of sleep efficiency, decrease of REM sleep frequency and time
Paroxysmal hemicrania	Fragmentation of sleep profile, decrease of REM sleep and total sleep time, increase of arousals in REM sleep
Tension-type headache	Early awakening, decrease of sleep stages 2–4, increase of sleep stage 1, decrease of total sleep time and sleep efficiency, increase of sleep movements
Trigeminal neuralgia	Increase of sleep latency, fragmentation of sleep profile, decrease of total sleep time and deep sleep stages, increase of movements in sleep, daytime sleepiness

REM, rapid eye movement.

Tension-type headache

Patients with TTH often suffer from sleep disturbances and awake in the morning without being able to fall into sleep again (41,56,57). In patients with chronic TTH, a reduction of sleep stages 2, 3, and 4, and a relative increase of sleep stage 1, a reduced sleep efficiency and total sleep time, and movements during sleep were observed; however, an association of chronic TTH and REM sleep could not be confirmed (58,59). However, there are only very few and old studies in TTH, and none of them has used modern-day technology. In summary, there is no robust evidence for a causal link between TTH and sleep disturbances as yet, but there is an urgent need for new sleep studies in properly classified TTH patients.

Cluster headache

In about 60% of all patients with cluster headache, the attacks occur predominantly in the night; in 8%, they occur exclusively at night. It has been reported that most attacks are triggered during REM sleep (34,37,60), but can also be triggered during NREM sleep (61). Kudrow et al. (34) showed that most attacks of episodic cluster headache, but not of chronic cluster headache, are associated either with REM sleep or with oxygen desaturation during sleep. The sleep profile is fragmented, the wake time is increased, sleep efficiency and frequency, and duration of REM sleep stages are decreased (34,61,62). However, the link between cluster headache and REM sleep could not be confirmed (63,64), and a large in-patient study confirmed that the affected REM sleep was without a particular temporal connection with nocturnal attacks (65). Furthermore, a substantially poorer sleep quality was reported in patients with cluster headache compared with controls, which was present not only inside the clusters, but also up to 1 year after their last cluster period (65).

The aetiological link between cluster headache and sleep is therefore not yet clarified. Probably different mechanisms play a role (66). Waldenlind et al. (67) detected decreased melatonin levels during acute cluster headache attacks but no relation of melatonin to the onset of the attack. Of interest, an association was found between cluster headache and sleep apnoea syndrome, but only in the active cluster episode, possibly due to involvement of the hypothalamus in the pathophysiology of cluster headache (68)

Paroxysmal hemicrania

Patients with paroxysmal hemicrania often show a fragmentation of sleep architecture with a decreased total sleep time, an increased REM sleep time, and an increase of arousals during REM sleep (33). If attacks of paroxysmal hemicrania start during sleep, they are typically linked to REM sleep or to the period directly following REM sleep (33). In some cases, the attacks are so closely linked to REM sleep that they are called 'REM sleep-locked' (33).

Medication overuse headache

Patients with medication overuse headache (MOH) often suffer from insomnia. In polysomnographic studies a fragmented sleep profile with decreased deep sleep stages and REM sleep and with frequent arousals during sleep can be found. After withdrawal therapy, an improvement of sleep profile has been observed (69).

Orofacial pain

Orofacial pain and trigeminal neuralgia are often associated with delayed sleep onset and with fragmentation of sleep leading to increased daytime sleepiness (70). In polysomnography studies, a reduced total sleep time, an increased number of wake periods and of movements during sleep, and a reduction in sleep stages 3 and 4 could be observed for patients with orofacial pain (70).

Headache as a symptom of sleep disorders

Sleep disorders can also cause headache as a symptom (71). An overview is given in Table 57.3. With respect to the association of morning headache and obstructive sleep apnoea syndrome (OSAS), conflicting results have been published. Some groups reported morning headache as a frequent symptom of OSAS, with an incidence of about 50% (69,72–76). However, other groupsreported that morning headache was not more frequent in patients with OSAS than in patients with other sleep disorders (but more common vs healthy subjects) (77–79). Loh et al. (74) showed a significant correlation between the severity of OSAS and the severity and frequency of morning headache, which normally had a duration < 30 minutes. Different reasons for morning headache in sleep disorders have been suggested: hypoxaemia/hypercapnia during the night; changes of intracranial pressure; cerebral vasodilatation; fragmentation of sleep (36,78). The night-time and morning headache in OSAS was treated in a majority of patients sufficiently by continuous positive airway pressure (CPAP) or by uvulopalatopharyngoplastic surgery, going along with normalization of fragmented sleep profile and oxygenation (69,74). Isolated snoring has also been detected as an independent risk factor for morning headache (75,80–82), including headache in their bedpartners (82).

Bruxism has a prevalence of 6–8% and is a frequent parasomnia (70). In up to 65% of all cases, it is associated with regular morning headache and neck pain and pain in the masticatory muscles (83,84). This headache maybe be treated by specific splints, botulinum toxin, and biofeedback, but clear evidence is lacking. Also benzodiazepines, muscle relaxants, tricyclic antidepressants, and beta blockers have been reported to be efficacious (70), although no proper controlled trials have been published. In addition, an independent association between bruxism and idiopathic headache disorders, in particular chronic migraine, has also been described (84,85).

Also, insomnia and periodic leg movements are associated with morning headache in about 25% of all cases (69,78). It was shown that headache in general, but not specifically migraine without or with aura, is associated with an about twofold increased risk for insomnia (86). This confirms previous studies that also linked sleep disturbances to headache in general (87). The underlying reason for this association can be speculated about in three ways. It might be that subjects with headache have a pathophysiology leading to both headache and insomnia; it might be that sleep disturbances are a trigger for headache in general; and it might be that headache induces insomnia. Further, a significant positive correlation of nightmares and morning headache has been found in older women, the causality of which has not yet been identified (88).

Table 57.3 Sleep disorders and disturbances leading to headache.

Sleep disorder	Headache
Obstructive sleep apnoea	Aspecific morning headache (normally < 30 minutes); isolated snoring
Bruxism	Aspecific morning headache, neck pain, pain in masticatory muscles
Insomnia	Aspecific morning headache
Fragmentation of sleep	Triggering migraine attacks

Association of headache disorders and sleep disorders

There are several significant associations between headache disorders and sleep disorders. It is still to be determined whether this association is due a common underlying pathogenetic mechanism or just a clinical observation.

In patients with migraine, an increased incidence of parasomnias, in particular of somnambulism, pavor nocturnus, and enuresis has been observed (50,89). In narcolepsy, a 2–5-fold increased incidence of migraine has been reported (54% of all cases) in one study (90), but this was not confirmed in another larger study, which only detected a mild association with unspecific TTH (91). A common underlying pathogenesis of both disorders seems unlikely. Studies on the association of narcolepsy with other headache disorders are lacking.

Recently, a significant association of migraine and REM sleep behaviour disorder (RBD) has been described; in particular, RBD was associated with a higher migraine-related disability (92). This association might be interpreted as brainstem dysfunction and increased brain excitability in migraine patients.

Restless legs syndrome (RLS) is a sleep disorder that has also been studied in different primary headache disorders. There is an unanimous finding that the prevalence of RLS is about threefold higher in migraine patients than in the normal population (93–98), and also in children (99). Co-occurrence of migraine and RLS leads to increased severity of both disorders (96). Also in patients with MOH, an increased incidence of RLS was observed (59). For cluster headache, no association with RLS could be found (94,96,100).

In observational studies it was reported that OSAS is present in more than 60% of all patients with cluster headache (34,101–103), but in a recent controlled in-patient study an equal prevalence of sleep apnoea in both patient and control groups was found, in contrast to the prior hypothesis of a connection between sleep apnoea and cluster headache (62). Some case reports suggested that cluster headache was improved when OSAS was effectively treated by CPAP (104–106), but controlled studies are lacking. Thus, the hypothesis that oxygen desaturation might play a role in the pathogenesis of cluster headache (74) remain to be properly confirmed.

In migraine, however, no significant association between OSAS and migraine was observed in a population-based study (107).

Sleep disturbances caused by headache medication

Several drugs with an impact on the central nervous system (CNS) can also interfere with the pattern of being awake or sleeping both during intake and during withdrawal. Therefore, it is important to study the potential effects of drug intake on sleep (108). This is particularly relevant for headache treatment as often both acute drugs and prophylactic drugs such as beta blockers, antidepressants, lithium, or anticonvulsants are taken, and these can affect sleep considerably (109). An overview of frequently used headache medication and their possible impact on sleep is given in Table 57.4.

Table 57.4 Frequently used headache drugs and their potential impact on sleep (alphabetical order).

Drug	Impact on sleep
Acetylsalicylic acid	Decrease of deep sleep, increase of sleep stage 1, mildly hypnotic
Amitriptyline	Sedation, decrease of REM sleep, prolonged REM sleep latency, reduction of apnoeas and hypopnoeas
Carbamazepine	Reduction of sleep stage 1 and REM sleep, prolonged REM sleep latency, increase of sleep stage 4, improved sleep continuity
Domperidone	–
Doxepin	Sedation, increase of deep sleep stages
Indomethacin	Sleepiness, somnolence, reduced coordination, calcium antagonist
Steroids	Increased vigilance, mild increase of sleep stage 1 and 4, decrease of REM sleep
Lithium	Decrease of REM sleep, prolonged REM sleep latency, increased somnambulism, provocation of RLS (?)
Metoclopramide	Sometimes frightening state with secondary low sleep quality
Metoprolol	Fragmentation of sleep, daytime sleepiness, vivid dreams
Phenylbutazone	Sleepiness, somnolence, reduced coordination
Propranolol	Fragmentation of sleep, daytime sleepiness, vivid dreams, reduction of bruxism
Topiramate	Somnambulism
Trazodone	Sedation, increase of deep sleep stages
Trimipramine	Increase of REM sleep
Valproic acid	Increase of deep sleep stages, decrease of REM sleep

REM, rapid eye movement; RLS, restless legs syndrome.

Analgesics

The intake of analgesics such as acetylsalicylic acid (ASA), phenylbutazone and indomethacin can lead to disturbances of sleep–wake transition. These disturbances are either linked to CNS side effects with somnolence, agitation, and so on, or linked to other side effects such as gastrointestinal impairment and impairment of ventilation (110). The intake of ASA leads to a significant reduction of sleep stage 4 and to a prolongation of sleep stage 2. Prostaglandins are involved in the regulation of sleep stages, an increase of prostaglandin D2, for example, increases NREM sleep stages. The impact of ASA on sleep can be modulated by inhibition of prostaglandin synthesis or by an increase of body temperature in the evening (111–114). In patients with insomnia, it could be shown that ASA leads to a reduction of wake phases during sleep (115). In higher doses (8–10 g), ASA can lead to a significant reduction of obstructive and mixed apnoeas with lower oxygen desaturation by stimulating effects on the upper airway muscles (116). Phenylbutazone and indomethacin in lower doses can induce sleepiness, somnolence, and impaired coordination (110).

Lithium

Lithium is used in the treatment of cluster headache and of hypnic headache (117,118). In healthy subjects, lithium taken over at least 2 weeks leads to decreased REM sleep and prolongs REM sleep latency, whereas total sleep time remains unchanged (119). In depressive patients, lithium is, in addition, associated with increase of deep sleep stages (119). The changes of sleep architecture by lithium are comparable to those caused by tricyclic antidepressants. It could be shown that somnambulism occurs up to three times more often than in the normal population or is reactivated by lithium alone or in combination with other psychotropic drugs (120). In one case report, lithium induced myoclonic jerks in the night and also RLS; after lithium withdrawal these symptoms disappeared completely (121).

Anticonvulsants

Daytime sleepiness and increased sleep are among the most frequently reported side effects of most anticonvulsants (108,110). Carbamazepine reduces sleep stage 1 and improves sleep continuity in patients with epilepsy (108). Also, in healthy subjects, carbamazepine reduces arousals during sleep and increased sleep stages 3 and 4 when taken over 5 days (122). After 10 days treatment, REM sleep was reduced and REM sleep latency was shortened (123). Harding et al. (124) could show that 1000 mg (but not 500 mg) valproic acid increases deep sleep stages and reduces REM sleep in healthy subjects. However, Drake et al. (48) found a mild reduction of deep sleep stages under the intake of valproic acid. For topiramate, some case reports on the induction of somnambulism have been published (125,126).

Antidepressants

The general effects on sleep of antidepressants used in headache treatment, in particular of the tricyclic antidepressants such as amitriptyline, are a suppression of REM sleep and a prolongation of REM sleep latency (108,110). However, there are some antidepressants (e.g. nefazodone and trimipramine) that might increase REM sleep (110). With respect to the influence of antidepressants on sleep continuity and NREM sleep, studies revealed conflicting results

(110). An abrupt withdrawal of antidepressants can lead to a REM sleep rebound with vivid dreams and poor sleep quality (108,110). Tricyclic antidepressants normally show a sedating effect; trazodone is one of the most sedating antidepressants and increases deep sleep stages. Like trimipramine and doxepin (110), it is often used in patients with severe insomnia (108). Both tricyclic antidepressants and selective serotonin reuptake inhibitors can lead to an occurrence or worsening of RLS, of period limb movements in sleep, and of REM sleep behaviour disorder (108,110). Tricyclic antidepressants reduce the number of apnoeas and hypopnoeas during sleep, and were used formerly in selected patients to treat OSAS; however, the responder rate was lower than 50% (127,128). Mirtazapine increased the sleep efficiency index, while decreasing the number of awakenings and their duration. The slow wave sleep time was increased, while the stage 1 sleep time was decreased significantly; there was no significant effect on REM sleep variables (129).

Beta blockers

Beta blockers can cause fragmentation of sleep and impair the duration of REM sleep in different ways. Many patients report daytime sleepiness, an increase of vivid dreams (so-called 'night terrors'), and hallucinations in the night. These sleep problems occur more frequently after the intake of lipophilic substances such as propranolol and metoprolol than after intake of hydrophilic substances such as atenolol (108). Propranolol was able to reduce bruxism in 72% of all cases (110).

Calcium antagonists

Different types of calcium antagonists (or calcium channel blockers) are used in the prophylactic treatment of migraine and cluster headache. A direct influence of calcium antagonists on sleep architecture has not been observed; patients do not report increased daytime sleepiness (130,131). There are observations that calcium antagonists induce changes of the pharmacokinetics of sedating drugs with prolongation of sleep when taken simultaneously (110).

Steroids

Steroids are used in the treatment of cluster headache and of giant cell arteritis. It is well known that a systemic high-dose application of steroids can lead to sleep disturbances and agitation, including mania (132). Polysomnographic longitudinal studies on the effect of low-dose steroids on sleep are lacking. A short-term intake of steroids, however, can improve sleep quality (108). Patients under steroids often report a subjective increase of wake time. In polysomnographic studies, a mild increase of sleep stage 2 and of deep sleep stages could be shown, whereas REM sleep was suppressed (108,110). This REM sleep suppression occurred under hydrocortisone but not under dexamethasone (108,110). REM sleep latency was even decreased under dexamethasone (108).

Antiemetics

The group of antiemetics comprises H_1-antihistaminic drugs, dopamine agonists, serotonin antagonists, and anticholinergic drugs. The influences of these drugs on sleep regulation are therefore very different (110,115). For the treatment of nausea in headache disorders, the D_2- and 5-HT_3-antagonist metoclopramide and the peripheral dopamine antagonist domperidone are used. Metoclopramide (and also sulpiride) do not show relevant sedating or narcotic properties when given in normal doses; in some case, even normal doses can induce anxiety, which can lead to secondary sleep disturbances (110). Domperidone is nearly exclusively acting at peripheral dopamine receptors and therefore does not exhibit CNS side effects (110).

Headache caused by sleep medication

In the treatment of insomnia, benzodiazepines and, in particular, benzodiazepine agonists such as zolpidem, zopiclone, and zaleplon are used as sleep drugs of first choice. These drugs rarely cause headache. Unspecific headache is the most frequent side effect of modafinil, which is used in the treatment of imperative sleep attacks in narcolepsy (133).

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58

Headache and fibromyalgia

Marina de Tommaso and Vittorio Sciruicchio

Introduction

Fibromyalgia (FM) is a chronic pain syndrome that causes disability and results in high medical costs (1,2). It is estimated to affect up to 5% of the general population in the USA and Europe (3–5). The diagnosis of FM is based on the American College of Rheumatology (ACR) criteria, which include a history of widespread pain lasting 3 months or longer (6). Widespread pain is defined as pain above and below the waist and on both sides of the body. In addition, axial skeletal pain (in the cervical spine, anterior chest, thoracic spine, or lower back) must be present According to the ACR criteria, a patient must have pain on digital palpation at 11 of 18 pre-designated sites, commonly referred to as tender points, to be diagnosed as having FM. Approximately 4 kg of pressure must be applied to a site and the patient must indicate that the site is painful (7). As a possible alternative to the ACR criteria for use in clinical settings, Wolfe et al. (8) proposed clinical diagnostic criteria for FM that do not rely on counting tender points. The proposed criteria take into account not only pain, but also other FM-related symptoms and are intended to assess the severity of those symptoms. To administer the Widespread Pain Index and Symptom Severity scale the physician asks the patient to report the location of any pain during the past week at 19 sites, including areas of the shoulders, arms, hips, legs, jaws, chest, abdomen, back, and neck. The Symptom Severity scale focuses on three physical symptoms, as well as somatic symptoms in general. Fatigue, waking unrefreshed, and cognitive symptoms are rated on the basis of the level of severity during the previous week. The new diagnostic criteria outline the importance of factors other than pain that may facilitate central sensitization and other mechanisms underlying this disabling condition.

Headache and fibromyalgia: a frequent comorbidity?

There are many conditions that co-exist with FM and some of these are now included in new diagnostic criteria (8). Examples of common comorbid disorders include mood or anxiety disorders, which can precede the development of FM (9,10), as well as other chronic pain syndromes, such as irritable bowel, interstitial cystitis or other painful bladder syndromes, chronic prostatitis or prostadynia, temporomandibular disorder, chronic pelvic pain, and vulvodynia (11,12).

Primary headaches have been rarely assessed in patients with FM, while more accurate evaluations were done in ascertaining the coexistence of FM in cohorts of patients with migraine and tension-type headache (TTH) (**Tables 58.1 and 58.2**). In **Table 58.1** studies assessing migraine and TTH comorbidities in cohorts of patients with FM are reported. In the study by Marcus et al. (13), 76 of 100 patients were affected by TTH or migraine. There are also studies examining migraine and TTH comorbidity in chronic fatigue syndrome (14), which reported both types of headache in the majority (84% migraine and 81% TTH) of patients. In our study of 199 patients with FM, 79 were affected by migraine (39%). These studies demonstrate the high frequency of migraine and TTH in FM and similar syndromes, such as chronic fatigue, and the potential importance of primary headache diagnoses for better management in view of mechanisms subtending these conditions and their association (15). Considering studies performed in primary headache populations, FM comorbidity was studied in migraine populations with a prevalence of 22% in episodic migraine (16) and 35.6% in transformed migraine (17). In a study of 217 consecutive headache patients, FM was observed in 36.4% of cases. The same study ascertained that TTH was the most common primary headache associated with FM, with a 59% prevalence versus episodic and chronic migraine (CM), which had a prevalence of 28.8%. The high prevalence of FM in both chronic TTH and CM suggests that diffuse muscle skeletal pain is a complicating condition for these two types of chronic headache (18). In a multicentre study on 1413 patients with migraine (19), a lower (10%) prevalance of FM was found, although the features of migraine (with or without aura, episodic or chronic) were not specified. In a more recent study conducted at our headache centre, we re-evaluated the prevalence of FM in a larger primary headache sample (1123 consecutive patients screened over 3 years) (20). We screened a total of 889 primary headache patients and the prevalence of FM was considered in regard to the main headache group and type according to the headache classification (International Headache Society 2004 classification). Considering the main headache groups (21), FM prevailed in TTH followed by the migraine group, and, in accordance with previous reports, FM was especially represented in chronic forms (**Table 58.2**). The frequency of FM (17.8%) found in the migraine group was almost the

Table 58.1 Prevalence of headache in fibromyalgia and chronic fatigue syndromes.

Reference	Type of study	Population	Type of diffuse pain or somatic symptoms syndrome	Prevalence of headache (%)
Aaron (85)	Observational	20 outpatients 25 outpatients	Fibromyalgia Chronic fatigue syndrome	4 TTH 23 TTH
Marcus et al. (13)	Observational	100 outpatients	Fibromyalgia	76 headache patients (48 migraine with and without aura; 18 TTH; 16 combined; 4 post-traumatic; 6 overuse headache)
Ravindran et al. (86)	Case–control	21 healthy subjects 68 patients	Chronic fatigue syndrome	16 migraine 28 TTH 11 both types of headache 84 migraine 81 TTH 67 both types of headache
de Tommaso et al. (15) Vij et al. (23)	Observational Cross-sectional survey	199 patients 1730 Patients	Fibromyalgia Fibromyalgia	39 7 migraine 55.8 migraine

TTH, tension-type headache.

same as previously reported (18), with a minimum in purely migraine with aura and a maximum in CM (Table 58.1).

The apparent discordance of FM prevalence across studies of migraine patients may be due to variability in applying FM diagnostic criteria, or to the lack of reporting or inattention to a history of widespread pain in medical visits where the primary focus is on headache. The more recent diagnostic criteria for FM (8) have not been yet applied to establish FM prevalence in primary headaches, although the general impression is that chronic TTH and CM are prone to FM comorbidity, while patients with sporadic migraine attacks—particularly those with aura—seem less affected by diffuse muscle skeletal pain. Studies have confirmed the high presence of FM in patients with migraine and its association with poorer quality of life, suggesting the potential importance of FM syndrome assessment in headache centres (22,23) (Table 58.2). A very low representation of patients with FM was found in other primary headache groups (trigeminal autonomic cephalgia and other forms) (Table 58.1). In light of our results and previous studies, no definitive conclusion about FM comorbidity can be drawn for other primary headache forms other than migraine and TTH. Rather, there is an impression of a low representation of FM, even in types with high headache frequency, such as chronic cluster headache, paroxysmal migraine, and hemicrania continua. Therefore, the frequency of headache does not appear to be the exclusive factor predicting comorbid FM

The utility of fibromyalgia assessment in primary headache patients: causes and principal features of comorbidity

FM is comorbid with other chronic pain conditions, including not only migraine and TTH, but also temporomandibular joint disorder, irritable bowel syndrome, and chronic fatigue syndrome. These conditions are all associated with hypersensitivity to painful or non-painful stimuli, and likely reduced endogenous pain inhibition (24). Hyperalgesia and allodynia are signs of central sensitization This phenomenon occurs in any type of pain—nociceptive or neuropathic—as well as when the pain threshold in the primarily involved areas becomes reduced, while in the adjacent zones stimuli that are not noxious become painful (25). Central sensitization may be an epiphenomenon of tissue or nervous system damage: in FM, peripheral changes at the muscular or cutaneous level are believed

Table 58.2 Prevalence of fibromyalgia in primary headaches (migraine and tension-type headache).

Reference	Type of study	Populations	Type of headache	Prevalence of fibromyalgia (%)
Peres et al. (17)	Observational	101 outpatients	Transformed migraine	35.6
Ifergane et al. (16)	Observational	94 outpatients	Migraine	22.2
Schur et al. (87)	Large-scale population study	3 982 twins individuals	Tension-type headache	Odd ratio (5.0)
Tietjen et al. (88)	Retrospective	223 outpatients	Migraine	37.21
de Tommaso et al. (18)	Observational	217 outpatients	Primary headaches	Migraine (including chronic migraine) 28.47 Tension-type headache 59.01
Tietjen et al. (19)	Observational	1413 outpatients	Migraine	10.0
de Tommaso et al. (20)	Observational	849 outpatients	Primary headaches	Migraine 17.8 Tension-type headache 35.06
Le et al. (89)	Large-scale population study	31 865 twin individuals	Migraine	20.0
Küçükşen et al. (22)	Observational	118	Migraine	31.4

Observational retrospective case–control and large-scale population studies published in the years 2000–13 were considered.

to provide noxious input, leading to permanent changes of nociceptive pathways, which result in chronic and disabling pain In migraine activation, of the trigeminovascular system (26) is believed to cause peripheral and central sensitization, with resultant spread of pain from intracranial structures to extracranial tissue, resulting in allodynia (27). Central sensitization is also believed to also be involved in the development of CM from episodic migraine (28). In this sense both migraine and FM may be characterized by a nociceptive pain that, regardless of its individual mechanism of initiation, results in a common mechanism of central sensitization. Chronic TTH may be subtended by pain mechanisms involving pericranial myofascial structures, and also resulting in central sensitization. In these patients measurements of pain tolerance thresholds and suprathreshold stimulation have shown the presence of generalized hyperalgesia (28). Other chronic pain syndromes, such as irritable bowel or chronic low back pain, may share this abnormal amplification of noxious inputs arising from visceral or local musculoskeletal structures (29). What is common in these diseases is the amplification of pain at the central level and its persistence despite the cessation of the initial cause. This shared mechanism may account for their mutual comorbidity. There are some mechanisms of pain modulation that are dysfunctional in these diseases. Neurophysiological techniques have shown several pain-processing abnormalities, which are common across migraine FM and other models of chronic, but not neuropathic, pain. Reduced habituation to repetitive painful stimuli may subtend an increase of noxious information at the cortical level favouring central sensitization (30). This pattern was detected in migraine and FM (30,31), as well as in other syndromes characterized by the absence of tissue damage and self- generating pain, such as cardiac X syndrome (32). Evidence has shown nociceptive system dysfunction at both central and peripheral levels in FM. Neuroimaging studies provide evidence for neural correlations to clinical findings of abnormal pain modulation in FM. Alterations in neural activation observed with functional imaging studies parallel structural finding, including a reduced volume of grey matter regions involved in the descending modulation of pain. Alterations of intrinsic connectivity of brain networks, and variations in metabolite levels along multiple pathways, have also been shown (33). Two studies performed on nociceptive-evoked responses obtained by concentric electrode or laser-evoked potentials and skin biopsy reported reduced amplitude of cortical responses co-existing with dysfunction of small myelinated and unmyelinated afferents (15,34). These studies have shown the heterogeneity of the FM syndrome, which is characterized by the co-existence of signs of central and peripheral nervous system involvement. The origin of peripheral afferent pathology is still unclear, but it may involve dysfunction of ion channels and persistent nociceptive fibre hyperactivation. Reduced habituation to painful stimuli seemed present in most patients with FM independently of the co-existence of peripheral afferent involvement. It was correlated with the severity of FM, confirming that the disturbance of pain processing at the central level may favour central sensitization and progression of clinical symptoms (15). The presence of migraine in patients with FM may contribute to altered pain processing at the central level, which may facilitate sensitization and persistence of diffuse pain.

The presence of FM in migraine, as well as TTH, patients indicates a special complexity in the therapeutic approach to these patients, which should take into account the presence of symptoms other than headache. Therapies should address potential shared mechanisms of increased headache frequency, the development of pericranial myofascial pain, and, spread of pain (35).

Clinical features of primary headache patients with fibromyalgia comorbidity

As we have previously shown (18) and further confirmed in a larger headache sample (Table 58.2), a combination of factors is associated with FM comorbidity headache frequency being the main, but not the only, cause. The phenotype of headache patients with FM comorbidity included anxiety (as measured by a self-rating anxiety scale) (36), pericranial tenderness (37), reduced physical performances—as measured by the Physical Component Summary of Short Form-36 (38)—and sleep disturbances showed by the Sleep Problems Index II (SLP9) score (39)

Pericranial tenderness is commonly observed in patients with chronic headache (40), and may represent a sign of permanent sensitization at cervical and trigeminal second-order nociceptive neurons subtended by a pathogenic process similar to that causing pain at tender points (41). Reduced habituation to pain common to migraine and FM (30,31) may facilitate central sensitization and myofascial pain persistence in the presence of other predisposing conditions, including anxiety and sleep disturbances. A self-sustaining circuit of increased headache frequency development of pericranial myofascial pain and persisting central sensitization with somatic diffusion of pain may explain FM comorbidity in both chronic TTH and CM (35). Sleep disturbance is a well-recognized factor in the FM syndrome (42), and our results confirm that in headache patients it is associated with generalized myofascial pain. The total number of sleep hours are not dissimilar between FM and non-FM patients, while the quality of sleep seems to be the discriminating factor for FM in our headache series, which is in accordance with our previous reports (Table 58.2) (18). Clinical and preclinical data agree that sleep disruption causes hyperalgesia, and despite widely distributed and overlapping neural networks regulate states of sleep and pain the brain mechanisms through which sleep and pain interact remain poorly understood (43,44). A significant association between severe sleep disturbances and chronic headache (45,46) and central sensitization (47) has further been reported. Poor quality sleep may promote the spread of myofascial pain in headache patients, but which sleep phase is more involved in the generation of widespread pain remains to be clarified.

Patients with FM exhibited higher depression and anxiety levels, but it was the latter feature that best discriminated patients with diffuse pain in our headache population (Table 58.2) (18). Mongini et al. (48) found that the presence of anxiety is associated with increased levels of muscle tenderness in the head and to and even greater extent in the neck, suggesting that it facilitates the evolution from episodic to chronic headache forms. In this way, anxiety may also facilitate diffuse myofascial pain and FM comorbidity in headache patients presenting with higher pericranial muscle tenderness. Patients with FM were also characterized by a reduced functioning in daily living inherent to physical abilities (Table 58.2) (18). This may suggests that persistent pericranial and somatic myofascial

pain have a consequence on motor performance and that physical inability may compromise quality of life in patients sharing FM comorbidity. In a recent study suicide risk was found to be elevated in migraine patients with comorbid FM (49,50).

Therapeutic approach in headache patients with fibromyalgia comorbidity

Presently, no guidelines are available regarding the treatment of associated FM in headache patients. The approach to these patients is particularly challenging because of their multiple clinical features and the absence of substantial evidence regarding therapeutic interventions (51). With regard to preventive approaches for migraine and TTH, amitriptyline is a drug of first choice (52), and there is also evidence for a positive effect in FM syndrome (53). It has mixed serotonergic and norepinephrine reuptake inhibitor properties, which may exert a variety of inhibitory effects on disturbed neurotransmission (54). Other antidepressants that are of proven efficacy in FM include duloxetine or milnacipran. There is limited evidence that these medications also have efficacy in migraine and TTH prevention (55–57). Their efficacy in reduction of migraine frequency was also observed in CM patients presenting with FM comorbidity (58). With regard to the antiepileptic drugs, topiramate and sodium valproate, which have proven efficacy in migraine (59–62), have poor evidence of action in FM (63). However, an improvement in FM symptoms was reported in migraine patients under topiramate treatment (64).

Beta blockers and calcium channels blockers, which are currently used in migraine prevention, have less of a theoretical basis for approaching FM comorbidity and may have unfavourable effects on depression (54,65).

Botulinum toxin

Botulinum toxin has been reported to relieve pain associated with a variety of conditions, including migraine headache. The presumed mechanism for headache prophylaxis is blockade of peripheral signals to the central nervous system, which inhibits central sensitization. Recently, its efficacy has been confirmed in CM (66,67), while its possible effect on associated FM symptoms remains uncertain. There is no evidence for the efficacy of botulinum toxin in chronic TTH (41) and FM (68), although the challenge in the future will be the better comprehension of botulinum toxin mechanism and its eventual action on central sensitization progression

Non-pharmacological approaches

The utility of non-pharmacological treatments, particularly psychological and physical therapy, as well acupuncture, have been shown in chronic TTH (41), as well as in FM (69). Previous experiences of the application of a self-management programme, including stretching and exercise to decrease strength and flexibility of muscles of the cervical and dorsal spine versus duloxetine treatment, showed that in patients with CM the comorbidity with FM may alter the outcome of pharmacological and non-pharmacological treatments on headache (58).

Another interesting potential approach to headache and FM treatment is the modulation of motor or dorso-lateral prefrontal cortex by means of repetitive transcranial magnetic or direct current The safety of single transcranial magnetic stimulation (TMS) in clinical practice, including as an acute migraine headache treatment, is supported by biological empirical and clinical trial evidence (70). Single-pulse TMS may offer a safe, non-pharmacological, non-behavioural therapeutic approach to the currently prescribed drugs for patients who suffer from migraine (71). Repetitive TMS (rTMS) of the prefrontal cortex also showed a positive effect in CM (72). rTMS of the primary motor cortex may be a valuable and a safe new therapeutic option in patients with FM. The analgesic effects induced by rTMS of the motor cortex has shown long-term efficacy in FM, for which it may be considered as a safe and new therapeutic option (73,74).

Fibromyalgia symptoms in juvenile migraine: similarity and differences

In the paediatric population, chronic and recurrent pain is increasingly being recognized as a significant health problem, but FM syndrome remains under-recognized, underdiagnosed, and ultimately undertreated. FM syndrome is a confusing and often misunderstood condition characterized by chronic pain, which appears in infancy and adolescence, more commonly in females (75,76). There are few studies of children with FM.

To determine the prevalence of FM, a previous study assessed 338 healthy schoolchildren: 21 children (6.2%) met the ACR criteria and received the diagnosis of FM (77).

Chronic widespread pain—particularly that evoked by pressing specific trigger points—sleep disturbances, fatigue, and mood disorders are the most frequent symptoms described in patients with FM (78). The causes, nature, and appropriate therapy for FM in adulthood are still not well defined, and we know even less about aetiology and treatment in children. In childhood, the underlying pathophysiology is presumably the same as adults, but the presenting symptoms are often different, especially in young children. Considering the chronic nature of symptoms, the severity of pain, and the disabilities correlated to this condition in adults, early diagnosis and treatment are fundamental in childhood.

One of the weakest point of the studies published so far is that the diagnosis of this syndrome is based on self-reported symptoms or on the 1990 ACR criteria for FM (6). The ACR criteria seem to be the most appropriate for affected adults, but may have limited applications in children. Therefore, these studies cannot give a precise image and the available data might underestimate the prevalence of FM in young people.

In their studies about young fibromyalgic patients, Yunus and Masi (75) suggested and applied the following diagnostic criteria for juvenile primary fibromyalgia:

1. Chronic widespread musculoskeletal pain located in at least three defined areas for > 3 months
2. Normal serology values
3. Pain evoked by pressure on at least five of 11 trigger points
4. At least three other criteria of sleep disturbances, irritable bowel syndrome, headache, feeling of soft tissue swelling, and fatigue.

Siegel et al. (79) noticed that widespread pain and sleep disorders are the predominant symptoms in children and that trigger points typically number < 10 in young patients. Reid et al. (80) confirmed the diagnostic accuracy of the criteria proposed by Yunus and Masi (75),

observing that in a group of 15 patients with peculiar fibromyalgic features all of them satisfied the criteria for juvenile primary FM proposed, whereas only 11 of 15 met the ACR criteria.

It is a commonly held opinion that the diagnostic criteria for juvenile primary FM must be distinguished from adulthood criteria. The criteria proposed by the ACR in 2010 seem to be more appropriate for the diagnosis of juvenile primary FM in infants and adolescents than the 1990 ACR criteria (8).

No studies have been reported so far about the comorbidity of FM and migraine in adolescents In only one study considering patients affected by frequent episodic TTH, a significant bilateral decrease of the pain threshold of temporal second metacarpal anterior tibial and superior trapezius muscles was demonstrated. The diffuse pain hypersensitivity observed in these patients and not noticed in the control population confirms the presence of central and peripheral sensitization in young patients diagnosed with TTH. The authors concluded that pain hypersensitivity also appears in young fibromyalgic patients, as already reported in previous studies about fibromyalgic adults, and questioned whether young patients affected by TTH might develop fibromyalgia as adults (81,82).

Other studies have reported how the severity and disability caused by chronic pain experienced by children might dramatically affect performance at school, having important repercussions on the persistence of chronic pain many years after diagnosis (83). In one study about quality of life, paediatric fibromyalgic patients reported a lower score than paediatric oncology patients undergoing chemotherapy, and also a lower score than young patients affected by chronic rheumatological diseases (84).

Conclusion

These data underline the importance of developing effective interventions for these disabling conditions The optimal clinical approach to FM should include the examination of concomitant comorbid conditions in order to improve patients' quality of life. In patients affected by primary migraine or TTH, we should also treat the associated symptoms (anxiety, sleep disturbances, and pericranial tenderness), which may promote comorbidity with FM. This may improve the efficacy of both pharmacological and non-pharmacological approaches, and may be a particularly important strategy in the management of children and adolescents.

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59

Visual snow

Gerrit L. J. Onderwater and Michel D. Ferrari

Introduction

Disturbances of vision have long been studied in the field of neurology. When looking at visual disturbances in association with headache disorders, the migraine aura is probably the most well-known. In approximately 30% of patients with migraine, migraine headache is accompanied by an aura phase, characterized by focal neurological symptoms, which usually develop gradually over 5–20 minutes and typically last for < 60 minutes and precede, or sometimes accompany, the headache (1–3).

Of these focal neurological symptoms, visual symptoms are the most common (4). Visual phenomena can include fully reversible positive and negative symptoms. Positive symptoms include flickering lights, spots, or lines, whereas negative symptoms include loss of vision, such as scotomata, visual field defects, or blindness. As stated in the previous paragraph, these symptoms usually last < 60 minutes. However, visual and other aura symptoms can last > 60 minutes in up to 25% of patients (3,5,6). According to the third edition of the International Classification of Headache Disorders (ICHD-3) criteria when aura symptoms typical for patients with migraine with aura persist for more than 7 days in the absence of radiological evidence of infarction, it should be classified as persistent aura without infarction. When due to an ischaemic brain lesion, it can be deemed a migrainous infarction (3). However, the visual disturbances do not always take a form that is typical for migraine and sometimes occur in non-migraine patients (7–20).

A condition known as Visual snow is such an atypical form of visual disturbance. First described by Liu et al. (7), various terms for visual snow have been used in the literature: primary persistent visual disturbance, persistent positive visual phenomena, and persistent migraine aura (7–20).

Visual snow is characterized by continuous visual disturbances in the form of countless tiny dots present in the entire visual field (7–20). It can have a major impact on patients' quality of life. Although these disturbances often are very bothersome and uncomfortable, they do not appear to interfere with visual function (7,14,15). Visual snow has been linked to migraine with persistent visual aura and to lysergic acid diethylamide (LSD) flashbacks (7,11,14,15). However, some physicians regard it as a trivial or psychogenic disorder (13,14,19,20).

Clinical phenotype

Visual snow was first described in 1995 by Liu et al.(7). In subsequent years several additional cases have been reported. Age of onset in the reported cases varied between 2 and 64 years, with a female predominance of 63%. The duration of the visual symptoms varied considerably, from 9 days to 30 years (7–18).

Visual snow is characterized by the persistence of positive visual phenomena. Patients generally describe the presence of multiple small particles, interpreted as television static, snow, lines of ants, or rain. The particles are generally white or black, and moving or flickering; however, multi-coloured visual disturbances have been reported (see **Figure 59.1**). The disturbing visual phenomena generally encompass the entire visual field and can also be visible when the eyes are closed. Patients frequently report variations in intensity of the visual disturbances with changes in ambient illumination. Additionally, the severity of the disturbances often varies with the nature of the environment. While looking at mono-coloured surroundings, such as white walls or the blue sky, the disturbances become more prominently visible. In some cases the visual disturbances preceded or occurred alongside a headache attack; however, this is not always the case (7–20).

Associated symptoms

Besides the multiple particles in the entire visual field, the visual disturbances are almost always accompanied with additional visual symptoms. These associated visual symptoms include palinopsia (afterimages from stationary and trailing from moving objects), nyctalopia (poor night vision), photophobia, and entoptic phenomena (occurring or originating inside the eye), such as floaters, self-light of the eye, blue field entoptic phenomenon, and spontaneous photopsia. However, patients with visual snow often also report non-visual symptoms, including bilateral tinnitus, concentration problems, lethargy, and irritability (14,15,19,20).

Relation with hallucinogenic drugs

Some hypotheses have linked visual snow to the use of certain hallucinogenic drugs, such as LSD-like substances or ecstasy. These

Figure 59.1 An illustration of a flower seen with (A) normal vision and (B) when suffering from visual snow, with multiple flickering dots in the entire visual field.

drugs are known to cause hallucinations, in some cases these hallucinations can persist for months or even years after drug use. This condition has been described as hallucinogen persisting perception disorder (HPPD) in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). According to the criteria, following the cessation of use of a hallucinogen, the patient should be re-experiencing one or more of the hallucinations that were experienced while intoxicated with the hallucinogen (e.g. afterimages, flashes of colour, and false perceptions of movement in the peripheral visual fields) (21).

However, case series of visual snow patients have shown that a minority of them have, indeed, used such recreational drugs or substances known to cause hallucinations (14,15). Additionally, visual snow also occurs in young children, who are highly unlikely to have used hallucinogenic drugs (13). Therefore, it is not likely that visual snow is strongly related to the use or cessation of use of hallucinogens.

Relation with migraine (aura)

Visual snow has been linked to migraine and migraine aura, in particular (7–20). However, currently, both conditions are still thought to be distinct disorders.

Research of large groups of patients with visual snow have shown that approximately 60% experience migraine attacks, of which around 50% have typical migraine aura (14,19), a proportion that is high compared to the general population (22). However, given that a substantial percentage of patients with visual snow do not have a history of migraine, it is unlikely that the two conditions are directly related to each other.

The clinical phenotype of migraine aura is commonly characterized by the occurrence of positive and negative visual symptoms often occurring unilaterally, whereas in visual snow almost uniformly only positive symptoms in the entire visual field are reported (4,7–20).

Additionally, most treatments used for treating frequent migraine aura or persistent migraine aura, such as acetazolamide and topiramate, are generally not successful in treating visual snow.

Associated symptoms such as floaters and blue field entoptic phenomenon occurring together with visual snow have been shown to be present independently of a history of migraine. On the other hand, associated symptoms like palinopsia, photophobia, nyctalopia, or tinnitus appear to be more frequently present in visual snow patients with a history of migraine (19), thereby making the whole spectrum of clinical phenotype of visual snow clearly different from migraine. Nevertheless, the co-occurrence with migraine (aura) might imply that both conditions share underlying pathophysiological mechanism(s).

Pathophysiology

The migraine aura is thought to arise from cortical spreading depression (CSD). In CSD, a wave propagates across the brain at 3–5 mm/minute and consists of an intense but transient (seconds) spike activity, followed by a transient depression of spontaneous and evoked neuronal activity lasting several minutes (23,24). However, the pathophysiology of visual snow and persistent aura appears to be distinct.

It has been suggested that persistent visual auras may be due to sustained reverberating waves of CSD (8,13,25). These reverberating CSD waves might be combined with steady-state hyperexcitability of the visual cortex, which was found in patients with persistent visual aura and visual snow when compared with episodic and chronic migraine patients in a magnetoencephalographic study (12,16). This is supported by results obtained using fludeoxyglucose ([18F]-FDG) positron emission tomography (PET) to compare a large group of 17 patients with visual snow with age- and sex-matched healthy controls. This study showed significant hypermetabolism in the area of the right lingual gyrus and the left anterior lobe of the cerebellum. The

changes found in the lingual gyrus are interesting as this brain area has been implicated in the modulation of visual processing (19,20).

However, individual patients with visual snow studied with PET or single-photon emission computed tomography (SPECT) revealed parietal–occipital hypoperfusion in some cases, but these results were inconsistent, as a number of patients showed no signs of hypoperfusion (7,12,18). Wang et al. (10) hypothesized that reverberating CSD waves might initiate the persistent visual symptoms and that in the process of reverberation, CSD waves may become disorganized. Therefore, visual symptoms would reflect formed and unformed CSD waves, and the positive phenomena could be a reflection of the preceding hyperactivity of CSD. With time, some alterations would become permanent, maybe due to neuroplasticity, which would then explain the intractability observed in some patients (10,16).

Investigations

Clinical investigations

Visual snow is diagnosed on patient history alone. In suspected cases, a thorough history should be taken together with a neurological examination, in order to rule out other causes for the visual disturbances. In visual snow the neurological examination typically is normal. Blood or cerebrospinal fluid examination rarely aid the diagnosis (7–20).

Ophthalmological investigations

In order to check that visual acuity is not affected and to rule out ophthalmological causes for the visual disturbances, such as retinal pathology, the patient should be seen by an ophthalmologist for a standard ophthalmological exam. Extended examination with electroretinography or visual evoked potentials generally does not contribute to the diagnosis (7–20).

Neurophysiology

Electroencephalography may be indicated to exclude occipital lobe epilepsy, especially when visual phenomena recur and consist of coloured and small circular patterns flashing or multiplying in a temporal hemifield. Flashing lights, non-circular patterns, and achromatic flickering lights, while uncommon, may also occur. Visual seizures usually last from seconds to 3 minutes, but may last up to 150 minutes (26).

Neuroimaging

Detailed structural neuroimaging in the form of computed tomography (CT) or magnetic resonance imaging (MRI) does not contribute to the diagnosis of visual snow (7–20). However, neuroimaging is recommended, especially if associated symptoms are present, in order to exclude structural abnormalities such as an arteriovenous malformation, occipital infarction, or demyelinating disease (27,28). MRI is much preferred over CT owing to higher resolution of the brain parenchyma. Nuclear imaging using SPECT or PET has been shown to detect areas of altered brain blood flow/metabolic activity in individual patients (7,12,18). However, as these alterations are far from uniform and cannot be used to make a diagnosis, it is generally not useful to use these techniques in the evaluation of these patients.

Diagnosis

Based on research with large patient groups, Schankin et al. (14) have proposed criteria for the diagnosis of visual snow, which are presented in **Box 59.1**. These criteria have been added to the Appendix of the ICHD- 3 (3). In these criteria, visual snow is defined as dynamic, continuous, tiny dots in the entire visual field lasting longer than 3 months, in association with at least two additional symptoms, not attributed to typical migraine visual aura or another disorder (14).

Management

Visual snow has been shown to be self-limiting in some cases (12,17). However, in most described cases it remains a chronic condition that is very difficult to suppress with drug or non-pharmacological treatment.

As a non-pharmacological approach, some patients with visual snow benefited from glasses with certain shades to make the visual symptoms less distinct.

A large variety of drugs from various classes has been tried such as antiepileptic drugs, calcium channel blockers, beta blockers, selective serotonin reuptake inhibitors, tricyclic antidepressants, and more (see **Table 59.1**) (7–14,16–19). Most treatments have no noticeable effect on the visual snow, or only influence the additional visual symptoms. Divalproex sodium, lamotrigine, topiramate, propranolol, sertraline, baclofen, naproxen, and verapamil in combination with aspirin and clonazepam have led to (partial) improvement of the visual snow in a minority of cases (7,8,11,14,19).

Invasive treatment with the use of occipital nerve injections did not lead to improvement (13).

To date, no randomized controlled trails have been performed for the treatment of visual snow. Therefore, the choice for a specific treatment should depend on patient factors and experience of the physician with certain drugs.

Box 59.1 Diagnostic criteria for visual snow listed in the Appendix of the ICHD-3

- **A** Dynamic, continuous, tiny dots in the entire visual field lasting longer than 3 months.
- **B** Presence of at least two additional visual symptoms of the four following categories:
  - **1** Palinopsia. At least one of the following: afterimages (different from retinal afterimages) or trailing of moving objects
  - **2** Enhanced entoptic phenomena. At least one of the following: excessive floaters in both eyes, excessive blue field entoptic phenomenon, self-light of the eye, or spontaneous photopsia
  - **3** Photophobia
  - **4** Impaired night vision (nyctalopia).
- **C** Symptoms are not consistent with typical migraine visual aura.
- **D** Symptoms are not better explained by another disorder.

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Table 59.1 Medication used for visual cases described in literature.

Drug class	Drugs
Calcium antagonists	Flunarizine, nifedipine, verapamil*
Prostaglandin synthase inhibitors	Aspirin
Selective serotonin reuptake inhibitors	Fluoxetine, sertraline*
Muscle relaxants	Baclofen*
Anxiolytics	Buspirone
Barbiturates	Phenobarbital
Tricyclic antidepressant	Amitriptyline, nortriptyline
Antiepileptic drugs	Carbamazepine, clonazepam,* divalproex sodium,* gabapentin, lamotrigine,* sodium valproate, topiramate*
Carbonic anhydrase inhibitors	Acetazolamide
Serotonin antagonist	Pizotifen
Beta blockers	Propranolol*
Anaesthetics	Ketamine
Non-steroidal anti-inflammatory drugs (NSAIDs)	Flurbiprofen, naproxen*
Serotonin and norepinephrine reuptake inhibitors	Duloxetine
Triptans	Sumatriptan
Antihistamines	Cyproheptadine
Central nervous system stimulants	Methylphenidate
Supplements	Coenzyme Q10, feverfew, magnesium oxide, riboflavin
Procedures	Occipital nerve injections with methyl prednisone and lidocaine

*Drugs that have led to (partial) improvement of visual snow, according to the literature.

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Index

Figures, Tables, and Boxes are indicated by *f*, *t*, or *b* following the page number.

5-HT receptors 35, 38, 130

abdominal migraine 461
abdominal pain, migraine comorbidity 112*t*, 115
abducens palsy 359
abscesses, cerebral 388*b*
acetaminophen *see* paracetamol
acetazolamide
  in episodic ataxia 84
  in hemiplegic migraine 80
  in idiopathic intracranial hypertension 361–2, 363*t*
  in intracranial neoplasia 431
  pre-epidural blood patch use 351
  use during pregnancy 364
  in vestibular migraine 133
acupuncture
  in chronic migraine 168, 280
  in tension-type headache 264
acute rhinosinusitis 411*t*–12
  medical therapies 414*t*
adalimumab 423
adenosine 514
adenovirus infections 379
adolescents *see* children
adverse effects
  beta blockers 154
  ergots 140
  headache as *see* toxic headaches
  indomethacin 205, 206
  onabotulinum toxin 159
  triptans 143
aerosinusitis 508
  see also airplane headache
Age, Gene/Environment Susceptibility (AGES)-Reykjavik study 27
aggravating factors 13–14
agitation, TACs 192, 204
air pollution 497*f*
airplane headache (AH) 372*b*–3, 413, 508
  clinical features 509–10*t*
  co-existing headache syndromes 510
  emotional impact 510*t*
  historical background 508–9
  ICDH-3 criteria 8*b*, 509*b*
  management 511–12
  onset in respect to flight timing 509*t*
  pathophysiology 511
Airy, George 54*f*
Airy, Hubert 52–4
  drawing of migraine aura 53*f*
alcohol-induced headache 369
Alice in Wonderland syndrome (AIWS) 248–9
allergic rhinitis 412, 414*t*
allergies, migraine comorbidity 115–16
allodynia 13, 62, 111, 114–15
  cluster headache 182
  fibromyalgia 524–5
  risk of migraine progression 278
all-trans retinoic acid 434
almotriptan 142, 143*t*
  in children 464
  pharmacokinetics 490*t*
alternating hemiplegia of childhood (AHC) 85
Alzheimer's disease, pain assessment 472
amaurosis fugax 421
American Academy of Neurology (AAN), guidelines on neuroimaging 18
American football, concussion risk 317–18
American Migraine Prevalence and Prevention (AMPP) study
  cardiovascular disease risk 101
  stroke risk 99
amitriptyline
  in cyclic vomiting syndrome 461
  in fibromyalgia 526
  in idiopathic intracranial hypertension 363*t*
  impact on sleep 518*t*
  migraine prevention 154*t*, 155
  in tension-type headache 262*t*
amlodipine 363*t*
amyl nitrate, in retinal migraine 95
analgesics
  in migraine 143–5, 144*t*
  see also non-steroidal anti-inflammatory drugs; opioids; paracetamol
ancient beliefs about headache 45–6
aneurysms
  association with SIH 351–2
  detection of 309–10
  treatment, effect on headache symptoms 338
  unruptured 338
  see also subarachnoid haemorrhage
angina, migraine as risk factor 101*t*
anginal headache (cardiac cephalalgia) 250, 311, 377*b*–8, 472
angiography
  aneurysm detection 309–10
  reversible cerebral vasoconstrictor syndrome 450*f*
angle closure glaucoma 396
antidepressants
  in fibromyalgia 526
  impact on sleep 518–19
  migraine prevention 155
  in tension-type headache 262*t*–3
antiemetics 139, 519
  with DHE 140
  in migraine 144, 145, 146
antiepileptic drugs (AEDs)
  in idiopathic intracranial hypertension 363*t*
  impact on sleep 518
  in migraine 121–2, 146, 154*t*, 155–6
  retinal migraine 95
  in SUNCT and SUNA 199
  in trigeminal neuralgia 240*t*–1
antimicrobial treatment
  in bacterial meningitis 386
  in rhinosinusitis 411
antinociceptive system 515
anxiety disorders
  airplane headache (AH) 510*t*
  CDH comorbidity 463
  fibromyalgia 525
  migraine anxiety-related dizziness 134
  migraine comorbidity 111, 112*t*, 113, 462–3
  see also psychiatric comorbidities
aphasia
  HaNDL 404, 406*f*
  hemiplegic migraine 77*f*
  migraine with aura 4*b*, 12, 24*f*
  pain assessment 472
  primary central nervous system vasculitis 421*t*, 425
aprepitant 461
Aretaeus 46
arousal streams 514
arterial dissection 7
arterial dysfunction, association with migraine 105
arteriovenous malformations 337–8
  headache as a symptom 335*t*
  headache mechanisms 341
arteritic anterior ischaemic optic neuropathy (AAION) 421
  fundoscopy 422
aseptic meningitis syndrome 387
aspirin
  association with MOH 287
  in giant cell arteritis 424
  impact on sleep 518
  in migraine 144
  international comparisons 287
  retinal migraine 95
  pregnancy and lactation 489*t*
  in tension-type headache 261*t*
asthma, migraine comorbidity 115–16
ataxia
  episodic ataxia type 2 84
  spinocerebellar ataxia type 6 84–5
Atherosclerosis Risk in Communities (ARIC) study 101, 103
  white matter lesions 28
atlantoaxial joint 253*f*
  neck–tongue syndrome 253–4
atmospheric trigger factors 67, 495–6
atopic disorders, migraine comorbidity 462
ATP1A2 mutations 75, 78, 121
  alternating hemiplegia of childhood 85
ATP1A3 mutations 85
atypical facial pain *see* persistent idiopathic facial pain
atypical odontalgia 244
audiograms 132
aura
  Alice in Wonderland syndrome 248–9
  clinical features 36
  cluster headache 182
  imaging studies 36
  mechanisms 36
  mimicking of TIA 98
  prolonged
  neuroimaging 20–2, 24*f*, 25*f*
  symptoms 12, 13*f*, 36, 62
  multiple 64–5
  sensory 64
  visual 53*f*, 54*f*, 55*f*, 56*f*, 62, 63*f*
  and visual snow 531
Australia, headache management 285
autoimmunity, role of *TREX1* 83
autonomic dysreflexia 376*b*
  ICDH-3 criteria 8
autonomic nervous system, role in cluster headaches 39
autosomal dominant polycystic kidney disease, CSF leaks 346
autosomal dominant retinal vasculopathy with cerebral leukodystrophy (AD-RVCL) 102*t*
azathioprine, in giant cell arteritis 423

back pain, migraine
comorbidity 112*t*, 115
baclofen 240*t*
bacterial meningitis
causative agents 385*t*
chronic headache 387*b*
clinical features 385
diagnosis 386
epidemiology 384
headache characteristics 385–6
ICDH-3 criteria 386*b*
prognosis 386
treatment 386
barbiturate hypnotics 145
basilar migraine 131
differentiation from HaNDL 405
see also migraine with brainstem aura
behavioural therapies 167–8, 263, 465
benign episodic pupillary mydriasis 392–3
benign occipital epilepsy of childhood (BOEP) 121
benign paroxysmal positional vertigo (BPPV) 131
children 129, 462
benign paroxysmal torticollis of infant 460, 461
beta blockers
in exertional headache 227
in headache secondary to intracranial neoplasia 431
in idiopathic intracranial hypertension 363*t*
impact on sleep 518*t*, 519
migraine prevention 153–4*t*
retinal migraine 95
in sexual headache 228
and sport 503
bevacizumab 434
bi-brachial amyotrophy 352
bidirectional comorbidity 110
biobehavioural therapy 465
biofeedback techniques
in migraine 167–8
in tension-type headache 263
bipolar disorder, migraine comorbidity 112*t*, 113, 478*t*
blip syndrome 249–50
blood-brain barrier disturbance
prolonged migraine aura 22, 25*f*
role in post-traumatic headache 318
body image distortion, Alice in Wonderland syndrome 248–9
borreliosis 379
botulinum toxin
in cervicogenic headache 327
in children 465
in fibromyalgia 526
in hemicrania continua 205
in idiopathic intracranial hypertension 362
in migraine 158–9, 279
in nummular headache 301
in older adults 473
in primary stabbing headache 217–18
in SUNCT and SUNA 199
in tension-type headache 262
in trigeminal neuralgia 241
brain abscess 388*b*
brain tumours *see* intracranial neoplasms
brainstem aura, migraine with 130–1
brainstem lesions 29, 30*f*
Brazil, headache management 285
Brown-Séquard, C.E. 49
brucellosis 379
bruxism 517
burning mouth syndrome 244–5
butalbital 145
association with MOH 287
butorphanol tartrate 145
butterbur 156–7, 167

C2 neuralgia 325
diagnosis 327
CACNA1A mutations 75, 78, 121, 460, 461, 462
episodic ataxia type 2 84, 130
mouse models 85
spinocerebellar ataxia type 6 84–5
CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) 29, 80–1, 100, 102*t*, 339
endothelial dysfunction 83
mouse models 85
caffeine
association with MOH 287
in hypnic headache 233–4
in spontaneous intracranial hypotension 350
in tension-type headache 261
calcitonin gene-related peptide (CGRP) 38, 70–1, 130
CGRP-induced headache 8, 370
CGRP-targeted therapies 147
in children 465
in chronic migraine 159–60, 280, 286
in cluster headache 186
effect of oestradiol 486
interictal levels 39
role in TACs
cluster headache 183
paroxysmal hemicrania 190
calcium channel blockers
in hemiplegic migraine 80
in idiopathic intracranial hypertension 363*t*
impact on sleep 519
in RCVS 6, 451
in retinal migraine 95
in sexual headache 228
in vestibular migraine 133
Calmeil, Louis-Florentin 49
caloric testing 131–2
CAMERA (Cerebral Abnormalities in Migraine, and Epidemiological Risk Analysis) MRI study 25, 100, 334
CAMERA-2 27
infratentorial hyperintense lesions 29
white matter lesions 27, 100–1, 115
Canada, headache management 285
cancer
migraine comorbidity 113*t*, 116
see also intracranial neoplasms
candesartan, migraine prevention 154*t*–5
carbamazepine
impact on sleep 518
in nummular headache 301
in SUNCT and SUNA 199
in trigeminal neuralgia 240*t*–1
carbon dioxide inhalation, in retinal migraine 95
carbon monoxide (CO)-induced headache 369
carbonic anhydrase 130
cardiac cephalalgia 250, 311, 377*b*–8, 472
cardiac X syndrome 525
cardiovascular disease
migraine as risk factor 100*b*, 101, 101*t*, 103, 334
mechanisms 103–5, 104*f*
risk management 105
screening for 351–2
carmustine 434
carotid artery dissection 395
cavernomas (cavernous haemangiomas) 335*t*, 338–9
celecoxib
in primary stabbing headache 217
see also non-steroidal anti-inflammatory drugs
Celsus 46
central sensitization 36, 524–5
role in chronic migraine 278
cerebellar tonsillar descent
cough headache 220–1, 222*f*, 223*f*
see also Chiari malformation type 1
cerebral abscess 388*b*
cerebral angiitis 335*t*, 339
cerebral blood flow, changes in systemic infections 379–80
cerebral microbleeds 101
cerebral oedema, reversible cerebral vasoconstrictor syndrome 449–50, 452*f*
cerebral venous sinus thrombosis (CVST) 311
association with CSF leaks 352
headache characteristics 335*t*, 337
headache mechanisms 341
cerebrospinal fluid (CSF)
in bacterial meningitis 386
CSF venous fistula 350
diversion procedures 363–4
in HaNDL 405
in hemiplegic migraine 77
leaks 346
complications 352
idiopathic intracranial hypertension 352
investigations 348–50
pathophysiology 346–7
screening for other disorders 351–2
treatment 350–1
types of 350
low pressure 221, 317
see also spontaneous intracranial hypotension
lymphocytosis 7, 8*b*
in PCNSV 425
pressure measurement 7*b*
idiopathic intracranial hypertension 360
production and flow 357
in spontaneous intracranial hypotension 348*t*
in subarachnoid haemorrhage 308, 309
TNF-α levels in NDPH 268
in tuberculous meningitis 389
in viral meningitis 387
cerebrovascular disorder-associated headache, ICDH-3 criteria 6
cervical artery dissection 311
association with migraine 104
headache characteristics 335*t*, 337
reversible cerebral vasoconstrictor syndrome 450
cervical arthritis 471
cervical joint arthrodesis 328–9
cervical nerve interventions 328
cervical nerves
anatomy 322–3
C2 neuralgia 325
role in migraine headache 37
cervicogenic headache 394*b*–5, 504
causes 325–6
clinical pathway 329
diagnosis 324–5
collapsed criteria 324*b*
ICDH-3 criteria 9*b*, 324*b*
diagnostic blocks 327
differential diagnosis 326–7
historical background 322
investigations 327
neuroanatomical basis 322–3
physiology 323
post-traumatic 317
studies in humans 323*f*–4
treatment 327
arthrodesis 328–9
C2–3 intervertebral disc surgery 328
cervical nerve interventions 328
greater occipital nerve interventions 328
CGRP *see* calcitonin gene-related peptide
chemokines, role in GCA 419, 420*f*
chemotherapy-related headache 434
Chiari malformations 442, 503
classification 443*t*
Chiari malformation type 1 222*f*
clinical features 442–3*t*
cough headache 220–1
headache types 444*t*
congenital and acquired causes 443*t*
diagnosis 444
differential diagnosis 443
epidemiology 442
ICDH-3 criteria 7–8*b*, 445*b*
pathophysiology 443
treatment options 444–5*f*
childhood periodic syndromes 460
abdominal migraine 461
benign paroxysmal positional vertigo 129, 131, 462
benign paroxysmal torticollis of infant 461
cyclic vomiting syndrome 461
infant colic 460–1
children 459
Alice in Wonderland syndrome 249

comorbidities 462–3
diagnosis 459–60
epidemiology 459, 460
fibromyalgia 526–7
hypnic headache 232
idiopathic intracranial hypertension 356–7
impact of headaches 463–4
juvenile bipolar disorders 463
migraine 459–60, 476
new daily persistent headache 268
primary stabbing headache 215, 216
treatment
acute 464
biobehavioural therapy 465
preventive 464–5
China, headache management 285
chinook winds, effect on migraine 496
chlorpromazine
in migraine 145, 146
in tension-type headache 261
chlorthalidone 363*t*
chocolate 67
chronic daily headache (CDH) 267, 284
comorbidities 463
management, international comparisons 284–5
psychiatric comorbidities 477
prognosis 479
suicide risk 479
see also chronic migraine; cluster headache; medication overuse headache
chronic fatigue syndrome, headache prevalence 524*t*
chronic migraine (CM) 61, 270*f*
Chiari malformation type 1 442–4
clinical features 285
epidemiology 285–6
historical background 275
ICDH-3 criteria 4, 5*b*, 275–6*b*, 277*b*
obstacles to management 276
pathophysiology 278
prevention 158–9
risk factors for 276, 277
Stilberstein–Lipton (revised) criteria 276*b*
treatment 278–80
international comparisons 286–7, 289, 294–5
see also migraine
chronic pain 15–16
chronic post-craniotomy headache (CPCH) 434–5
chronic rhinitis/rhinosinusitis 411*t*–12
medical therapies 414*t*
chronic tension-type headache (CTTH) 270*f*
comorbidities 260
ICDH-3 criteria 260*b*
see also tension-type headache
cilostazol 71
circadian sleep drive 514
citalopram 363*t*
CLOCK gene 515
clomiphene 199
clomipramine 262
cluster headache 12–13, 177
associations
OSAS 518
pituitary tumours 432–4, 435*t*
sleep disturbance 516
autonomic symptoms 13
clinical examination 183
clinical features 179*t*, 182–3
temporal pattern 13*f*
diagnosis 184
ICDH-3 criteria 178*b*, 183*b*
differential diagnosis 183, 184
hypnic headache 233*f*
paroxysmal hemicrania 192, 193*t*
epidemiology 178–9, 182
genetics 183
histamine-induced 370
historical background 54, 182
mechanisms 39–40
melatonin secretion 515
nitroglycerin-induced 368
in older adults 471
pathophysiology 183
secondary 178
post-traumatic 317
and sport 503–4
treatment 180, 289
acute 184–5
CGRP-targeted therapies 186
international comparisons 289, 290, 296–7
nerve blocks 185
neuromodulation 185–6
prophylactic 185
weather-related effects 494
cluster tic syndrome 208
descriptions in the literature 209*b*
pathophysiology 208–9
treatment 209
cocaine-induced headache 369–70
cocktail headache 369
codeine
association with MOH 287
in migraine 145
coenzyme Q10 (ubiquinone) 154*t*, 157–8, 166
cognitive impairment, pain assessment 472
cognitive-behavioural therapy (CBT)
in children 465
in tension-type headache 263
COL4A1 mutations 83
colloid cyst of the third ventricle 431–2
combat-related PTH 318
combination analgesics
in migraine 145
in tension-type headache 261
COMOESTAS project 279
comorbidities
in children 462–3
migraine
asthma and allergies 115–16
cancer 113*t*, 116
diabetes 113*t*, 116
epilepsy 120–4
gynaecological disorders 116
mechanisms 110, 111*f*
movement disorders 115
multiple sclerosis 113*t*, 116
obesity 113*t*, 116
pain disorders 114–15
psychiatric disorders 111, 113, 477–8*t*
sleep disorders 113–14
studies 110, 112*t*
syncope 115
vertigo 128–34
in older adults 473
psychiatric disorders 475
epidemiology 476
historical background 475
in migraine 477–8
pathophysiological bases 475–6
prognosis 479
risk factors 476–7
suicide risk 478–9
substance dependence and abuse 479
tension-type headache 260
computed tomography (CT)
CT angiography 309–10
in giant cell arteritis 422
idiopathic intracranial hypertension 359–60
myelography (CTM) 349–50
pseudo-SAH 385*f*
in reversible cerebral vasoconstrictor syndrome 450*f*
in spontaneous intracranial hypotension 349
in subarachnoid haemorrhage 307–9
see also neuroimaging
concussion 314
conjunctival injection
cluster headache 182
hemicrania continua 204
paroxysmal hemicrania 191
SUNCT 197, 199
connective tissue disorders
CSF leaks 346
screening for 351–2
corneal neuropathy 397
cortical spreading depression (CSD) 17
as a cause of headache 37
connection between migraine and epilepsy 120–1
mechanisms 36–7
role in ischaemic stroke 104
and visual snow 531–2
corticosteroids *see* steroids
cough headache 220, 312
aetiology 220
Chiari malformation type 1 443, 444*t*
clinical features 221
differential diagnosis 221–2*f*
epidemiology 220
ICDH-3 criteria 221*b*
neuroimaging 221–2*f*
pathophysiology 220–1
treatment 222–3
cranial nerve abnormalities, idiopathic intracranial hypertension 359
cranial neuralgias, in older adults 471
craniotomy, post-operative headache 434–5
crossed-cerebellar diaschisis 21–2
cryptococcal meningitis 389
CSNK1D mutations 79
mouse models 85
cyclic vomiting syndrome 461
cyclophosphamide 425
cyproheptadine 461
cytarabine 434
cytokines
role in GCA 419, 420*f*
role in post-traumatic headache 318

Dandy, Walter 356
daytime sleepiness, migraine comorbidity 112*t*, 114
decongestants, in airplane headache 511
deep brain stimulation (DBS) 185–6, 289
dementia, pain assessment 472
dendritic cells, role in GCA 419, 420*f*
dengue virus infections 379
dental caries 400
dental pain 399–400
depression
CDH comorbidity 463
fibromyalgia 525
migraine comorbidity 111, 112*t*, 462, 478*t*
see also psychiatric comorbidities
desipramine 363*t*
dexamethasone
in bacterial meningitis 386
in migraine 146
IV treatment 146
menstrual migraine 487
in status migrainosus 145
see also steroids
dexketoprofen 145, 146
combination with triptans 143
see also non-steroidal anti-inflammatory drugs
DFNA9 (autosomal dominant nonsyndromic sensorineural deafness 9) 130
dialysis headache 374*b*, 471–2
diclofenac potassium
in migraine 144
in tension-type headache 261*t*
see also non-steroidal anti-inflammatory drugs
digital subtraction angiography (DSA) 309–10
reversible cerebral vasoconstrictor syndrome 450*f*
digital subtraction myelography (DSM) 350
dihydroergotamine (DHE) 140*t*–1
in abdominal migraine 461
in cluster headache 185
in status migrainosus 147
see also ergots
diphenhydramine
in migraine 145
in tension-type headache 261
diplopia
giant cell arteritis 422
idiopathic intracranial hypertension 358
disc displacement, temporomandibular joint 401
discogenic pain 326

disorders of homeostasis, headaches
due to 371, 378*b*
cardiac cephalalgia 250, 311, 377*b*–8
dialysis headache 374*b*
fasting-associated 377*b*
hypertension-associated 374*b*–6
hypothyroidism-associated 376–7*b*
hypoxia and hypercapnia-associated 371*b*–4
ICDH-3 criteria 371*b*
divalproex sodium *see* sodium valproate
diving headache 373*b*, 497, 510
dizziness, definition 128
dopamine agonists, in TACs 433
domperidone 36
impact on sleep 518*t*, 519
pregnancy and lactation 489*t*
dopamine, role in migraine 35–6
dopamine antagonists 145, 146
dopaminergic dysfunction 112*t*
dorsolateral pons, role in migraine headache 37
doxepin, impact on sleep 518*t*
'drop attacks' 13
drug-related headaches *see* toxic headaches
dry eye 396–7
Du-Bois Reymond, Emil 49
duloxetine 526
dural venous sinus stenting 362–3
duration of pain 12, 13*f*
cluster headache 182
cough headache 221
hemicrania continua 203
hypnic headache 230
migraine 61
paroxysmal hemicrania 191
primary stabbing headache 216
SUNCT 197, 200*f*
trigeminal neuralgia 200*f*, 237

eclampsia 376*b*
Egypt, ancient beliefs about headache 45
Ehlers-Danlos syndrome, CSF leaks 346
elderly *see* older adults
electroencephalography (EEG)
in HaNDL 405, 406*f*
in migraine 34, 120
hemiplegic 77
electromagnetic spectrum 499*f*
electromagnetism, sensitivity to 498
electromyography (EMG) biofeedback 263
eletriptan 142, 143*t*
pharmacokinetics 490*t*
endothelial dysfunction
association with migraine 105, 340
RVCL-S 83
endothelial progenitor cells (EPCs) 83
epicrania fugax 250–1
Epidemiology of Vascular Aging (EVA) study 27
infarct-like lesions 100
white matter lesions 28, 100–1
epidural blood patches (EBPs) 350–1
epigenetics 487
epilepsy, migraine comorbidity 120, 124
classification issues 122–4, 123*b*
drug treatment 121–2
hemiplegic migraine 77
shared pathophysiology 120–1
episodic ataxia type 2 (EA2) 84, 130
episodic ataxia type 6 (EA6) 84
episodic tension-type headache
ICDH-3 criteria 260*b*
see also tension-type headache
Epstein–Barr virus (EBV) infection 379
as trigger for NDPH 268
eptinezumab 160, 280
erenumab 159, 280, 286
ergots/ergotamine 140*t*–1
historical background 56
in older adults 473
in sexual headache 228
and stroke risk 103
eslicarbazepine 199
ESR1 polymorphism 487
etanercept 423
etoricoxib 217
Eulenburg, A. 49
Eurolight initiative 286
European Federation of Neurological Societies (EFNS), guidelines on neuroimaging 18
exercise *see* physical activity
exertional headaches 220, 312, 444*t*
cardiac cephalalgia 250, 311, 377*b*–8
classification 502–3*b*
ICDH-3 criteria 227*b*
clinical features 226
diagnosis 226
differential diagnosis 226
cough headache 221
epidemiology 225–6, 502
historical background 225
investigations 503
pathophysiology 227, 504–5
prognosis 228
reversible cerebral vasoconstrictor syndrome 447–54
treatment 227
in elite sportspeople 504
exogenous hormone-induced headache 484
exploding head syndrome (EHS) 251
exposure to substances *see* toxic headaches
eye pain *see* ocular pain
eyelid oedema 198

facial flushing
cluster headache 182
diving headache 373*b*
hemicrania continua 204, 393*b*
paroxysmal hemicrania 191
phaeochromocytoma 375
facial pain
association with intracranial neoplasia 433*t*
ICDH-3 classification 9–10
lacrimal neuralgia 252–3
in older adults 471
secondary to intracranial tumours 435–7
see also glossopharyngeal neuralgia; painful post-traumatic trigeminal neuropathy; persistent idiopathic facial pain; trigeminal neuralgia
familial advanced sleep phase syndrome (FASPS)
migraine comorbidity 112*t*, 114
familial hemiplegic migraine (FHM) 75, 339
associations
EA2 84
epilepsy 121
SCA6 84–5
ICDH-3 classification 4
mouse models 85
subtypes 78*b*
see also hemiplegic migraine
family history 15
fampridine 84
fasting-associated headache 377*b*
fatigue, as a migraine trigger 69–70
female hormones
as a migraine trigger 69
and vestibular migraine 130
see also hormone-related migraine
Fernel, Jean (Fernelius) 47
fever 379
giant cell arteritis 421
HaNDL 404
feverfew 154*t*, 167
fibrin glue (fibrin sealant) 351
fibromyalgia 523
central sensitization 524–5
in children 526–7
clinical features 525–6
comorbidities 112*t*, 115, 523, 524–5
association with headache disorders 523–4*t*
management 526
first of Ramadan headache 377
flunarizine 154*t*, 157
fluoxetine 363*t*
Foley, Joseph 356
food, trigger factors 67–8
fortification spectra 12
Fothergill, John 48
fremanezumab 159–60, 280, 286
frequency of pain 12, 13*f*
cluster headache 182
hemicrania continua 203
hypnic headache 230
migraine 61
paroxysmal hemicrania 191
primary stabbing headache 216
SUNCT 197
trigeminal neuralgia 238
frequent headaches 284
see also chronic migraine; cluster headache; medication overuse headache
Frisén system, papilloedema 359
frovatriptan 142, 143*t*
combination with NSAIDs 143
migraine prevention 488
pharmacokinetics 490*t*
fungal infections 379
intracranial 389*b*
furosemide, in idiopathic intracranial hypertension 362, 363*t*

gabapentin
in hemicrania continua 205
in idiopathic intracranial hypertension 363*t*
in nummular headache 301
in older adults 473
in post-craniotomy headache 435
in primary stabbing headache 217
in SUNCT and SUNA 199
in trigeminal neuralgia 240*t*, 241
gadolinium, intrathecal use 349–50
galcanezumab 160, 280, 286
Galen 46, 67
gamma knife surgery 242
Gasserian ganglion interventions 241–2
gastric bypass surgery 363*t*
gender ratios
cough headache 221
exploding head syndrome 251
giant cell arteritis 418
HaNDL 403–4
hemicrania continua 203
hypnic headache 230
idiopathic intracranial hypertension 356
migraine 61, 69
psychiatric comorbidities 476
retinal 93–4
new daily persistent headache 269
nummular headache 298
paroxysmal hemicrania 190
primary stabbing headache 215
red ear syndrome 254
reversible cerebral vasoconstrictor syndrome 447
sexual headaches 226
tension-type headache 259
trigeminal neuralgia 237
genetic factors 75
in migraine 340–1
menstrual-related 487
vestibular 129–30
in TACs
cluster headache 183
see also monogenic syndromes
genetic testing 78
Germany, headache management 284–5
MOH 288
GiACTA trial 424
giant cell arteritis (GCA) 270*f*, 271, 339, 418, 471
clinical features 421*t*–2
diagnosis 422–3*b*
epidemiology 418
fundoscopy 422
ICDH-3 criteria 421*b*
management 423–4
neuroimaging 422
pathogenesis 418–19, 420*f*
pathology 418, 419*f*
risk factors for 418, 419
temporal artery biopsy 422
temporal artery swelling 422*f*
ginger, migraine prevention 167
glaucoma 396
Global Drug Reference Online 504
glossodynia (burning mouth syndrome) 244–5
glossopharyngeal neuralgia 242–3
glucocorticoids *see* steroids

glutaminergic system
effect of oestradiol 486
effect of progesterone 487
glyceryl trinitrate (GTN), as a migraine trigger 70
GnRH analogue treatment 490
goserelin (Zoladex) 490
Gowers, William 54
Graves' disease 397
greater occipital nerve interventions
in cervicogenic headache 328
nerve block 185
diagnostic use 327
in paroxysmal hemicrania 193
in SUNCT and SUNA 199
stimulation 169
in cluster headache 186
noxious, pattern of referred pain 323
Greece, ancient beliefs about headache 45–6
gynaecological disorders, migraine comorbidity 112*t*, 116

haemodialysis 374*b*, 471–2
Haemophilus influenzae type b meningitis 384
haemorrhagic stroke
headache as a prognostic factor 339–40
headache as a symptom 335*t*, 336
stabbing headache 216
migraine as risk factor 25, 99–100*b*, 101*t*
reversible cerebral vasoconstrictor syndrome 449–50, 452*f*
see also stroke
Hall, Marshall 49
hallucinations 64
hallucinogen persisting perception disorder (HPPD) 531
hallucinogenic drugs 530–1
halo sign, giant cell arteritis 422
Hamilton Depression Rating Scales 477
HANAC (hereditary angiopathy, nephropathy, aneurysms, and muscle cramps) 83
HaNDL (headache with neurological deficits and CSF lymphocytosis) 7, 8*b*, 387
aetiology and pathophysiology 404, 405*f*
clinical features 403–4
differential diagnosis 404–5
hemiplegic migraine 77–8
epidemiology 403
historical background 403
ICDH-3 criteria 404*b*
investigations 405, 406*f*
treatment 405
hangover headache 369
Harlequin syndrome 251–2*f*
Harris, Wilfred 54
HCRTR2 183
head trauma *see* traumatic brain injury
headache diaries 138
headache mechanisms 34
cluster headache 39–40
migraine
aura 36
chronic changes 39
cortical spreading depression 36–7
genetic factors 34
headache phase 37–9
neurophysiological changes 34
postdrome 39
premonitory phase 35–6
sensory sensitivity 39
serotonin hypothesis 34–5
Head-HUNT study 490
hearing loss
DFNA9 130
Ménière disease 129, 130, 131
hemicrania continua (HC) 177, 178*b*, 203, 203–6, 206, 270*f*, 392, 393*b*
aetiology 204
association with pituitary tumours 432–4, 435*t*
clinical features 179, 203–4
diagnosis 178*b*, 204*b*, 205
differential diagnosis 180
paroxysmal hemicrania 192, 193*t*
epidemiology 178–9, 203
family history 204
ICDH-3 classification 5
pathophysiology 204
post-traumatic 317
prognosis 205
treatment 180, 205
hemicrania epileptica 122
hemiplegic migraine (HM) 75
associations
EA2 84
epilepsy 77
SCA6 84–5
CSF analysis 77
diagnosis 75–6, 80*b*
differentiation from HaNDL 77–8, 405
EEG 77
genetic testing 78–9
ICDH-3 criteria 76*b*
mouse models 85
neuroimaging 76–7*f*
pathophysiology 78, 79*f*
prophylaxis 80
subtypes 78*b*
treatment 79–80
herpes simplex virus (HSV) 379
herpes zoster
meningoencephalitis 217
postherpetic neuralgia 394, 394*b*
high-altitude headache 371–2*b*, 497, 498*f*, 510
ICDH-3 criteria 8
HIHRATL (hereditary infantile hemiparesis, retinal arteriolar tortuosity, and leukoencephalopathy) 102*t*
Hildegard of Bingen 46*f*
histamine-induced headache 370
historical background
ancient times 45–6
eighteenth century 47–9, 50*f*, 51*f*
middle ages 46–7
nineteenth century 49, 52–4
scientific revolution 47
twentieth century 54–6
history-taking 12
diagnosis based on 15–16
family history 15
headache history
associated features 13
frequency and duration 12, 13*f*
headache characteristics 12
length of illness 12
precipitating or aggravating factors 13–14
previous treatments 14
quality 13
relieving factors 14
time and mode of onset 12
past health 14–15
personal background 15
HIV infection 389
homeostasis, disorders of *see* disorders of homeostasis
hormone replacement therapy (HRT) 484, 490
hormone-related migraine
characteristics and prevalence 484–5*t*
pathophysiology 485–7
treatment
hysterectomy and ovariectomy 490
menstrual migraine 487–8
perimenopausal migraine 490
during pregnancy and lactation 488–9*t*
Horner's syndrome 13
carotid artery dissection 395
Horton, Baynard 54
hot-dog headache 368
humidity, effect on migraine 496
hypercapnia-associated headaches 371*b*
diving headache 373*b*
sleep apnoea headache 373*b*–4
hyperdense paraspinal vein sign 350
hypermobility syndrome 268
hyperprolactinaemia 348
hypertension-associated headaches 374*b*–6
phaeochromocytoma 375*b*
hypertensive crisis 375*b*
hypertensive encephalopathy 375*b*–6
hypnic headache (HH)
in children 232
clinical features 230–1*t*
comorbidities 231
diagnosis 232–3*f*
differential diagnosis 233
cluster headache 233*f*
migraine 232*t*
disease course 232
epidemiology 230
historical background 230
ICDH-3 criteria 5*b*, 231*b*
in older adults 471
pathophysiology 232
polysomnography 231
treatment 233–4
hypothalamic deep brain stimulation 185–6
hypothalamus
role in cluster headaches 39
role in hemicrania continua 204
role in hypnic headache 232*f*
role in migraine 35, 278
role in SUNCT and SUNA 199
role in TACs 180, 433
cluster headache 183
paroxysmal hemicrania 190–1
sleep and pain functions 515*t*
hypothyroidism-associated headache 376–7*b*
hypoxia-associated headaches 371*b*
airplane travel-associated 372*b*–3
high-altitude headache 371–2*b*
sleep apnoea headache 373*b*–4
hysterectomy 490

ibuprofen
in migraine 144
in tension-type headache 261*t*, 262
see also non-steroidal anti-inflammatory drugs
ICD-11 10
'ice cream headaches' 13
'ice pick pains' 13, 61
primary stabbing headache 216, 392
ictal epileptic headache (IEH) 121, 122, 123*b*, 124
idiopathic intracranial hypertension (IIH) 270*f*, 271
associations and comorbidities 357*b*, 360–1
clinical features 358–9, 360*f*
diagnostic criteria 357*b*
epidemiology 356–7
historical background 356
ICDH-3 criteria 7*b*
investigations
lumbar puncture 360
neuroimaging 359–60*f*
mechanism of headache 358
pathophysiology 357–8
in pregnancy 364
prognosis 364
treatment 361
diuretics 361–2, 363*t*
of headache 362, 363*t*
surgical management 362–4
therapeutic lumbar puncture 362
topiramate 362
weight loss 361
Idiopathic Intracranial Hypertension Treatment Trial (IIHTT) 358, 361–2
idiopathic orbital inflammation (IOI) 396
ignition hypothesis, trigeminal neuralgia 237
imipramine 363*t*
India
ancient beliefs about headache 45
MOH management 288
indomethacin
adverse effects 205, 206
impact on sleep 518
in cough headache 222–3
in exertional headache 227
in hypnic headache 234
in migraine 145
in nummular headache 301
in paroxysmal hemicrania 433
in primary stabbing headache 217
in sexual headache 228
see also non-steroidal anti-inflammatory drugs
indomethacin-sensitivity
hemicrania continua 205
paroxysmal hemicrania 191, 193
infant colic 460–1
infarct-like lesions 100, 103*f*

infections
intracranial *see* intracranial infections
systemic *see* systemic infection-associated headaches
inflammatory orbital pseudotumour (idiopathic orbital inflammation) 396
infliximab 423
influenza 379
infraorbital nerve block 199
infraorbital nerve dehiscence 413
infratentorial hyperintense lesions (IHLs) 30*f*
insomnia, migraine comorbidity 112*t*, 114
integrated headache care 168
interferon-γ, role in GCA 419, 420*f*
interictal headache 122
interleukins
role in GCA 419, 420*f*
role in post-traumatic headache 318
internal carotid artery pathology 326–7
International Burden of Migraine Study (IBMS) 286
International Classification of Headache Disorders (ICHD) 3
changes in ICHD-3
cranial neuralgias and facial pain 9–10
primary headache disorders 4–6
secondary headache disorders 6–9
classification of TACs 177–8*b*
hierarchical organization 4
migraine in children 460
relation to ICD-11 10
validity testing 10
intra-arterial vasodilator therapy, RCVS 453–4
intracerebral haemorrhage (ICH)
headache as a prognostic factor 339–40
headache as a symptom 335*t*, 336
stabbing headache 216
migraine as risk factor 25, 99–100*b*, 101*t*
see also stroke
intracranial hypertension
Chiari malformation type 1 444*t*
see also idiopathic intracranial hypertension
intracranial infections 384
bacterial meningitis 384–7
cerebral abscess 388*b*
in HIV-positive patients 389
subdural empyema 389
tuberculous meningitis 389
viral encephalitis 388*b*
viral meningitis 387*b*–8
intracranial lesions, temporal pattern of headache 13*f*
intracranial neoplasms 471
colloid cyst of the third ventricle 431–2
epidemiology 428
facial pain 433*t*, 435–7
headache
clinical features 429–30*t*, 431*t*
ICHD-3 codes 429*t*
ICHD-3 criteria 430*b*
influencing factors 428–9*t*
pathophysiology 428
treatment 430–1
investigations 430
leptomeningeal carcinomatosis 432
pituitary apoplexy 432
pituitary tumours
trigeminal autonomic cephalalgias 432–4
treatment-related headache 434–5
intranasal sumatriptan 141
intranasal triptans 142
intrathecal chemotherapy 434
irritable bowel syndrome (IBS) 525
migraine comorbidity 115
ischaemic stroke
headache as a prognostic factor 339–40
pathophysiology 341
headache as a symptom 334–5*t*
pathophysiology 341
stabbing headache 216
and migraine, pathophysiology 340–1
migraine as risk factor 22–3, 25, 99, 100*b*, 101*t*, 104, 334
risk management 105
reversible cerebral vasoconstrictor syndrome 449–50, 452*f*
thunderclap headache 311
see also stroke
isoproterenol 95
Israel, ancient beliefs about headache 45
Italian Project on Stroke in Young Adults (IPSYS) 99

Jaccoud, S.F. 49
Janetta procedure 199
Japan, MOH management 288
jaw claudication 421
juvenile bipolar disorders (JBD) 463

ketamine 80
ketoprofen 261*t*
see also non-steroidal anti-inflammatory drugs
ketorolac 145, 146
see also non-steroidal anti-inflammatory drugs (NSAIDs)
Kinkelin, Jules Pelletan de 49

lacrimal neuralgia 252–3
lacrimation
cluster headache 182
hemicrania continua 204
paroxysmal hemicrania 191
SUNA 198
SUNCT 197, 199
lactation
migraine prevalence 485
migraine treatment 489
lacunar infarctions 335
lamotrigine
in SUNCT and SUNA 199
in trigeminal neuralgia 240*t*, 241
lasmiditan 38
lateral atlanto–axial joint blocks 326*f*
diagnostic use 327
lateral atlanto–axial joint pain 325
Latham, P.W. 49
laugh headache 442, 444*t*
Le Pois, Charles 47
legionella infection 379
length of illness 12
leptomeningeal carcinomatosis 432
leptospirosis 379
lidocaine, in SUNCT and SUNA 199
lifestyle
history-taking 15
trigger factors for migraine 69–70
lifestyle modification 138
children 465
lithium
cluster headache prophylaxis 185
in hypnic headache 233
impact on sleep 518
Liveing, Edward 52*f*
low back pain 525
migraine comorbidity 112*t*, 115
low-pressure headache
Chiari malformation type 1 444*t*
ICDH-3 criteria 7*b*
lumbar puncture
in bacterial meningitis 386
as cause of headache 434
in HaNDL 405
in idiopathic intracranial hypertension 360
in spontaneous intracranial hypotension 348*t*
therapeutic 362
see also cerebrospinal fluid
lumboperitoneal shunts (LPS) 363–4
Luther, Martin 47
lysine clonixinate 146

magnesium, migraine prevention 146, 154*t*, 166, 488
magnetic resonance imaging (MRI)
angiography 310
blood-brain barrier disturbance 25*f*
CADASIL 81*f*
Chiari malformation type 1 444*f*
colloid cyst of the third ventricle 431
in giant cell arteritis 422
in HaNDL 405
in idiopathic intracranial hypertension 359–60*f*
infratentorial hyperintense lesions 29, 30*f*
in leptomeningeal carcinomatosis 432
in migraine
hemiplegic 76–7*f*
infarct-like lesions 103*f*
prolonged aura 24*f*
in migrainous infarction 19–22, 20*f*, 21*f*, 22*f*, 23*f*, 99*f*
cerebellar 26*f*
myelography 349–50
in PCNSV 425
in reversible cerebral vasoconstrictor syndrome 449–50*f*, 452*f*
in RVCL-S 82*f*
in spontaneous intracranial hypotension 349
subclinical findings 30
venography 360*f*
white matter lesions 27–8, 102*f*, 103*f*
see also neuroimaging
malaria 379
manual therapy 327
MAP0004 140–1
Marfan syndrome 352
CSF leaks 346
medication overuse
in chronic migraine 111, 278
definition 277
in post-traumatic headache 319
medication overuse headache (MOH) 4, 479
causes 287
in children 464
epidemiology 276–7
international comparisons 287
ICDH-3 criteria 8*b*, 277*b*
management 278–80
international comparisons 287–9, 295–6
prevention 139, 362
sleep disturbance 517
medication-induced headaches 370
see also toxic headaches
medieval beliefs about headache 46–7
Mediterranean spotted fever 379
MELAS (mitochondrial myopathy with encephalopathy, lactic acidosis, and stroke) 84, 102*t*, 339
melatonin 515–16
and childhood migraine 461
in hemicrania continua 205
in hypnic headache 234
in primary stabbing headache 217
memory disturbance 64
Ménière disease 129, 131
genetic factors 130
meningeal irritation 348
meningitis
bacterial
causative agents 385*t*
chronic headache 387*b*
clinical features 385
diagnosis 386
epidemiology 384
headache characteristics 385–6
ICDH-3 criteria 386*b*
prognosis 386
treatment 386
cryptococcal 389
and new daily persistent headache 270
tuberculous 389
viral 387*b*–8
diagnostic criteria 388*b*
meningococcal meningitis
clinical features 385
epidemiology 384
see also meningitis, bacterial
menopause 490
effect on migraine 485, 486*f*
menstrual cycle 485–6*f*
relationship to migraine incidence 69*f*
menstrual-related migraine 69, 72, 484
pathophysiology 485–7
treatment 487–8
frovatriptan 142

meperidine 146
Mesopotamia, beliefs about headache 45
metabolic syndrome 360
metalloproteinases (MMPs), role in GCA 419, 420*f*
metamizole
in migraine 146
in tension-type headache 261
methazolamide 363*t*
methotrexate
in giant cell arteritis 423
intrathecal 434
methylprednisolone
in giant cell arteritis 423
in PCNSV 425
methysergide
in cluster headache 185
in sexual headache 228
metoclopramide
impact on sleep 518*t*, 519
in migraine 144, 145
IV treatment 146
during pregnancy and lactation 489*t*
in tension-type headache 261
metoprolol
impact on sleep 518*t*, 519
see also beta blockers
mianserin 262
microvascular decompression 242
mid-segment facial pain 413
migraine 3
abdominal 461
cardiovascular disease risk 100*b*, 101*t*, 334
mechanisms 103–5, 104*f*
risk management 105
central sensitization 525
in children 459–60, 463–4
chronic *see* chronic migraine
classification 13*f*
ICDH-3 4, 5*b*
clinical features
aura symptoms 62–5
duration 61
frequency 61
gender ratio 61
location 62
premonitory symptoms 62
temporal pattern 13*f*
complications 65
cerebral microbleeds 101
infarct-like lesions 100
see also stroke risk
differential diagnosis
cluster headache 184
hemicrania continua 205
RVCS 451
epidemiology 485*f*
family history 15
genetic factors 75, 340–1
historical background
ancient beliefs 45–6
eighteenth century theories 47–9
medieval beliefs 46–7
nineteenth century theories 49, 52–4
scientific revolution 47
twentieth century theories 54–5
hormone-related characteristics and prevalence 484–5*t*
pathophysiology 485–7
treatment 487–90
monogenic syndromes 339
alternating hemiplegia of childhood 85
CADASIL 80–1
COL4A1-related 83
episodic ataxia type 2 84
hemiplegic migraine 75–80
MELAS 84
mouse models 85
RVCL-S 81–3
spinocerebellar ataxia type 6 84–5
neuroimaging 17
brainstem lesions 29–30*f*
indications for 17–18, 19, 31
premonitory phase 35
in prolonged aura 20–2, 24*f*, 25*f*
white matter lesions 27–9*f*, 28*f*
in older adults 470–1
ophthalmoplegic 10
pain remapping 400
post-traumatic 317, 318
prognosis 65
retinal 92–5
secondary to intracranial tumours 437
and sport 503
stages of an attack 62*f*
stroke risk 18–19, 31, 98, 99–100*b*, 101*t*, 340
clinical ischaemic stroke 22–3, 25
haemorrhagic stroke 25
pathophysiology 340–1
subclinical stroke 25, 26*f*, 27
trigger factors 67, 68*t*
atmospheric 67
clinical implications 71–2
female hormones 69
food 67–8
lifestyle factors 69–70
patient perceptions 71
pharmacological 70–1
physical activity 504
psychosocial stress 68*f*–9
weather-related effects 494–6
clinical studies, difficulties with 498–500
white matter lesions 100–1
see also aura; childhood periodic syndromes; migraine comorbidities and associations; migraine management; migraine mechanisms; migraine prophylaxis
migraine anxiety-related dizziness (MARD) 134
migraine aura-triggered seizure 123*b*
migraine chronification, triad of 111, 113*f*
migraine comorbidities and associations 103
asthma and allergies 115–16
cancer 113*t*, 116
cavernomas 338–9
cervical artery dissection 337
Chiari malformation type 1 442–3, 444*t*
in children 462–3
chronic rhinitis 412
diabetes 113*t*, 116
epilepsy 120, 124
classification issues 123*b*
drug treatment 121–2
shared pathophysiology 120–1
exertional headaches 226
fibromyalgia 523–4*t*
gynaecological disorders 116
hypnic headache 231
mechanisms 110, 111*f*
medication overuse headache 479
movement disorders 115
multiple sclerosis 113*t*, 116
obesity 113*t*, 116
pain disorders 114–15
patent foramen ovale 105–6
primary stabbing headache 216
psychiatric disorders
bipolar disorder 111, 113, 475, 477–8, 478*t*
depression 478*t*
epidemiology 476
historical background 475
pathophysiological bases 475–6
prognosis 479
risk factors 476–7
suicide risk 478–9
sleep disorders 113–14, 516, 517
studies 110, 112*t*
syncope 115
vertigo 128
see also vestibular migraine
visual snow 531
migraine management 138
acute treatment
analgesics and NSAIDs 143–5
barbiturate hypnotics 145
calcitonin gene-related peptide antagonists 147
in children 464
dopamine antagonists 145
drug choice 139*b*
ergots 140*t*–1
home rescue 145–6
hospital rescue 146
neuromodulation 147
opioids 145
specific drugs 139–44, 140*t*
in status migrainosus 146–7
strategies 138–9
timing of 139
triptans 140*t*, 141–3
goals 138–9
international comparisons 287
during lactation 488–9*t*
menstrual-related migraine 487–8
non-pharmacological 165
perimenopausal 490
during pregnancy 488–9*t*
migraine mechanisms 35*f*
aura 36
chronic changes 39
cortical spreading depression 36–7
genetic factors 34
headache phase
anatomy 37–8
pharmacology 38
prostaglandins 38–9
role of CGRP 38
role of PACAP 38
neurophysiological changes 34
postdrome 39
premonitory phase 35–6
sensory sensitivity 39
serotonin hypothesis 34–5
migraine prophylaxis 153, 158–9
acupuncture 168
anticonvulsants 154*t*, 155–6
antidepressants 155
behavioural therapies 167–8
beta blockers 153–4
candesartan 154*t*–5
CGRP-targeted therapies 159–60
in children 464–5
coenzyme Q10 154*t*, 157–8, 166
duration 153
efficacy and tolerability 152–3
exercise 167
flunarizine 154*t*, 157
guidelines 154*t*
herbal medicines 166–7
petasites 154*t*, 156–7
indications for 152
during lactation 489*t*
magnesium 166
menstrual-related migraine 488
multidisciplinary approach 168
naproxen 154*t*, 157
neuromodulation 160–1, 168–71
non-pharmacological 157–8, 160–1, 165–71
during pregnancy 489*t*
riboflavin 154*t*, 157, 165–6
thiotic acid 166
topiramate 158
migraine with aura, ICDH-3 classification 4*b*
migraine with brainstem aura 130–1
migraine-triggered seizures (migralepsy) 121, 122
migrainous infarction 19, 98, 336, 340
case series 20*b*
diagnostic criteria 19*b*
mechanisms 19–20
neuroimaging 19, 20*f*, 21*f*, 22*f*, 23*f*, 99*f*
migrainous thoracalgia 250
military combat-related PTH 318
milnacipran 526
mindfulness-based therapy
in children 465
in tension-type headache 263
mirtazepine
impact on sleep 519
in tension-type headache 262*t*–3
MIST (Migraine intervention with STARFlex Technology) trial 105–6
mixed rhinitis 412
medical therapies 414*t*
modafinil 519
mode of onset 12, 15–16
Moldova, headache management 285
Möllendorf 49
monogenic syndromes 75, 76*f*, 339
alternating hemiplegia of childhood 85
CADASIL 80–1
COL4A1-related 83
episodic ataxia type 2 84
hemiplegic migraine 75–80
MELAS 84
mouse models 85
RVCL-S 81–3
spinocerebellar ataxia type 6 84–5

Monro–Kellie hypothesis 346–7
motor disturbance 64
  hemiplegic migraine 75–80
movement disorders, migraine comorbidity 112*t*, 115
MTHFR 487
mucosal contact points 413
multidisciplinary approach 168
multiple headache diagnoses 3
multiple sclerosis
  differentiation from HaNDL 405
  migraine comorbidity 113*t*, 116
  trigeminal neuralgia 239, 241
muscle pain 401
muscle relaxants 272
muscular examination 401
myalgia 401
mycoplasma infections 379
myelography 349–50
myocardial infarction, migraine as risk factor 100*b*, 101*t*
myofascial pain 401
  fibromyalgia 525

nabilone 279–80
nadolol
  in idiopathic intracranial hypertension 363*t*
  migraine prevention 154
  see also beta blockers
nalbuphine 146
naproxen
  in migraine 144
  combination with triptans 143
  migraine prevention 154*t*, 157
  in tension-type headache 261*t*
  see also non-steroidal anti-inflammatory drugs
naratriptan 142, 143*t*
  pharmacokinetics 490*t*
  pregnancy and lactation 489*t*
  in sexual headache 228
  see also triptans
narcolepsy 517
  migraine comorbidity 112*t*, 114
nasal congestion
  cluster headache 182, 183*b*
  hemicrania continua 204
  paroxysmal hemicrania 191
  SUNCT 197
nasal headaches
  differential diagnosis 414
  historical background 409
  ICDH-3 criteria 410*b*
  management 414*t*–15
  McAuliffe and Wolfe's experiments 409, 410*b*
  nature of 409
  potential mechanisms 414*f*
  specific disorders 410–11*t*
  acute and chronic rhinosinusitis 411–12
  airplane headaches 413
  chronic rhinitis 412
  infraorbital nerve dehiscence 413
  mid-segment facial pain 413
  mucosal contact points 413
  vacuum headaches 412–13
nasal mucosa, turbinates or septum, headache attributed to 410*b*, 411*t*
nasal polyps 411, 412
  medical therapies 414*t*
National Institutes of Health (NIH) classification 3
nausea and vomiting 13
  cluster headache 182
  HaNDL 404
  see also antiemetics
neck rigidity 13
neck–tongue syndrome 253–4, 325
neuralgic pain 13
neuroimaging 17, 18–19
  bacterial meningitis 386
  CADASIL 81*f*
  Chiari malformation type 1 444*f*
  colloid cyst of the third ventricle 431
  cough headache 221–2*f*
  giant cell arteritis 422
  HaNDL 405, 406*f*
  hypnic headache 232*f*
  idiopathic intracranial hypertension 359–60
  indications for 17–18, 19, 31
  infratentorial hyperintense lesions 29–30*f*
  intracranial neoplasia 430
  migraine 38
  aura 36
  chronic changes 39
  evidence for serotonin hypothesis 34–5
  hemiplegic 76–7*f*
  infarct-like lesions 103*f*
  postdrome 39
  premonitory phase 35
  prolonged aura 20–2
  retinal 94
  migrainous infarction 19, 20*f*, 21*f*, 22*f*, 23*f*, 99*f*
  paroxysmal hemicrania 190
  PCNSV 425
  posterior circulation infarcts 26*f*
  reversible cerebral vasoconstrictor syndrome 448*f*, 449–50, 452*f*
  RVCL-S 82*f*
  spontaneous intracranial hypotension 349–50
  subarachnoid haemorrhage 307–9
  subclinical findings 30
  trigeminal neuralgia 240
  visual snow 531–2
  white matter lesions 27–9*f*, 28*f*, 102*f*, 103*f*
neuroleptics 145, 146
neuromodulation 147
  in children 465
  in cluster headache 185
  in fibromyalgia 526
  in hemicrania continua 205
  migraine prophylaxis 160–1, 168–71, 286
  in paroxysmal hemicrania 193
neurotransmission, effects of oestradiol 486
neurotropin 301
neurovascular disorders
  headache as a prognostic factor 341
  headache as a risk factor 334
  pathophysiology 340–1
  headache as a symptom 334, 335*t*
  arteriovenous malformations 337–8
  cavernomas 338–9
  cerebral angiitis 339
  cerebral venous sinus thrombosis 337
  cervical artery dissection 337
  genetic cerebral angiopathies 339
  intracerebral haemorrhage 336
  ischaemic stroke and TIA 334–5
  migrainous infarction 336
  pathophysiology 341
  reversible cerebral vasoconstrictor syndrome 337
  subarachnoid haemorrhage 336–7
  unruptured aneurysms 338
  see also stroke
new daily persistent headache (NDPH)
  clinical features 269
  diagnostic criteria 267
  ICDH-3 criteria 5, 6*b*, 268*b*
  epidemiology 267
  historical background 267
  investigations 272
  mimics 269–71
  pathophysiology 269
  pre-existing headache disorders 269
  prognosis 272
  treatment 272
  triggers 267–8
nifedipine 217
nimodipine 228
nitric oxide (NO), as a migraine trigger 70
nitric oxide donor-induced headache 368, 371
nitric oxide pathways, effect of oestradiol 486–7
nitroglycerin (NTG) headache 368, 371
nociception 514–15
  dysfunctional 525
nonallergic rhinitis 412
  medical therapies 414*t*
Nonne, Max 356
non-steroidal anti-inflammatory drugs (NSAIDs)
  adverse effects 205, 206
  impact on sleep 518
  in exertional headache 227
  in hypnic headache 234
  in idiopathic intracranial hypertension 362
  impact on sleep 518
  in migraine 143–5, 144*t*, 145, 146, 154*t*, 157, 488
  children 464
  combination with triptans 143
  in nummular headache 301
  in older adults 472–3
  in paroxysmal hemicrania 433
  pregnancy and lactation 364, 489*t*
  in primary stabbing headache 217
  in sexual headache 228
  in tension-type headache 261*t*
Northern Manhattan Study (NOMAS) 27
  infarct-like lesions 100
  stroke risk 99
  white matter lesions 28, 100–1
nortriptyline 363*t*
nose
  innervation of 410
  mucosal contact points 413
  see also nasal congestion; nasal headaches
NOTCH3 mutations 80, 81, 339
numbness 64
nummular headache (NH) 270*f*
  clinical examination and investigations 299
  clinical features 298–9
  pressure pain threshold topography 300*f*
  topography 299*f*
  diagnosis 301
  epidemiology 298
  ICDH-3 criteria 5*b*, 301*b*
  past history 299
  pathophysiology 299
  primary and secondary forms 300
  prognosis 301
  secondary to intracranial tumours 437
  treatment 301
nystagmus 133
  benign paroxysmal positional vertigo 131
  vestibular migraine 131

obesity
  in idiopathic intracranial hypertension 356, 357, 360
  effect of weight loss 361
  migraine comorbidity 113*t*, 116, 462
obstructive sleep apnoea (OSAS) 517
  and cluster headache 518
  and hypnic headache 231
  migraine comorbidity 112*t*, 113, 114
occipital nerve stimulation (ONS)
  in Chiari malformation type 1 445
  in chronic migraine 280
  in cluster headache 289
  in hemicrania continua 205
occipital neuralgia 325
octreotide 433
ocular pain 392
  ophthalmic and orbital causes 395–8
  primary headache disorders 392–3*b*
  secondary headache disorders 393–5, 394*b*
ocular surface disease 396–7
oculomotor RPON 393
oestradiol
  actions 486
  effects on neurotransmission 486
  effects on vasculature 486–7
  migraine prevention 488
  role in menstrual migraine 484
oestrogen withdrawal headache 69, 72, 484
olcegepant 147
older adults 470
  cranial neuralgias 471
  epidemiology of headache 470–1
  hypnic headache 471
  migraine 470–1
  pain assessment 472
  secondary headache disorders 471
  tension-type headache 471
  treatment of headache 472–3
  trigeminal autonomic cephalalgias 471
onabotulinum toxin *see* botulinum toxin
ondansetron 434
onset of headache 12, 15–16
ONSTIM (Occipital Nerve Stimulation for the Treatment of Intractable Migraine) 169

oophorectomy 490
ophthalmoplegic migraine 393
  ICDH-3 criteria 10
opiate receptors, effect of oestradiol 486
opioids
  in migraine 145–6
  in tension-type headache 261
opportunistic infections 389
optic nerve sheath abnormalities, SIH 349
optic nerve sheath fenestration (ONSF) 362, 363
optic neuropathy 358
oral contraceptive use 484
  migraine prevention 488
  in migraine with aura 105
  stroke risk 23
orbital findings, SIH 349
orbital tumours 397–8
orexinergic system
  role in cluster headache 183
  role in hypnic headache 232
orexins 35, 514, 515
orofacial pain 399
  sleep disturbance 517
  temporomandibular disorder 400–2
  tooth pains 399–400
orthostatic headache 347
orthostatic oedema 360–1
osteoarthritis (OA), temporomandibular joint 401
otoacoustic emissions 132
ovariectomy 490
oxcarbazepine
  in SUNCT and SUNA 199
  in trigeminal neuralgia 240*t*, 241
oxetorone 234
Oxford Vascular Study (OXVASC) 99
oxygen inhalation
  in cluster headache 185
  in hangover headache 369

pain assessment, older adults 472
pain disorders, migraine comorbidity 112*t*, 114–15
pain remapping 400
painful post-traumatic trigeminal neuropathy 243–4
PAMINA study 69
Panayiotopoulos syndrome 122
papilloedema 7*b*
  colloid cyst of the third ventricle 431
  idiopathic intracranial hypertension 359, 360*f*
paracetamol
  in exertional headache 227
  in idiopathic intracranial hypertension 362
  in migraine 144
  international comparisons 287
  in older adults 472
  pregnancy and lactation 489*t*
  in tension-type headache 261*t*
paraesthesiae 64
parasitic infections 389*b*
parasomnias 517
paroxetine 363*t*
paroxysmal hemicrania 190
  association with pituitary tumours 432–4, 435*t*
  chronicity 192
  clinical features 179*t*, 191
  diagnosis 193
  ICDH-3 criteria 178*b*
  differential diagnosis 180, 192, 193*t*
  trigeminal neuralgia 239*t*
  epidemiology 178–9, 190
  family history 192–3
  functional imaging studies 190
  interictal pain 191
  migrainous features 191–2
  natural history 193
  pathophysiology 190–1
  periodicity 192
  secondary 192
  post-traumatic 317
  sex distribution 190
  sleep disturbance 517
  treatment 180, 193
  triggers 192
paroxysmal hemicrania tic syndrome 209–10*b*
Parry, Caleb Hillier 48
patent foramen ovale (PFO) 20, 25, 65, 105–6
patient education 263
periaquductal grey matter
  role in migraine headache 37
  sleep and pain functions 515*t*
peri-ictal headache 122
perimenopausal migraine 490
perimesencephalic SAH 307, 310, 336
periodontal disease 400
peripheral nerve stimulation (PNS) 168–70
persistent idiopathic facial pain 10, 243
personal background 15
petasites 154*t*, 156–7, 167
phaeochromocytoma-associated headache 375*b*
phenylbutazone 518
phenytoin
  in SUNCT and SUNA 199
  in trigeminal neuralgia 241
phonophobia 62, 141, 179*t*, 191–2, 193*t*
  airplane headache 509
  cardiac cephalalgia 250
  cervicogenic headache 324*b*
  cocaine-induced headache 370
  HaNDL 403
  hemicrania continua 204, 205
  new daily persistent headache 267, 269
  spontaneous intracranial hypotension 348
  stabbing headache 216
phosphodiesterase (PDE) inhibitor-induced headache 369
photosensitivity 62, 141, 179*t*, 191–2, 193*t*
  cardiac cephalalgia 250
  cervicogenic headache 324*b*
  HaNDL 403
  hemicrania continua 204, 205
  link between migraine and epilepsy 121
  mechanisms 39
  new daily persistent headache 267, 269
  spontaneous intracranial hypotension 348
  stabbing headache 216
physical activity
  benefits 502
  as a migraine trigger 70
  migraine prevention 167
  see also exertional headaches; sporting activity
physical therapy
  in fibromyalgia 526
  in tension-type headache 263
pineal cyst 431
Piorry, Pierre-Adolphe 49
pituitary adenylate cyclase-activating peptide (PACAP) 38, 71
pituitary apoplexy 311, 432
pituitary tumours
  association with TACs
  cluster headache 178
  management 433–4
  paroxysmal hemicrania 192
  pathophysiology 433
  epidemiology 432–3
platelet-derived growth factor (PDGF), role in GCA 419, 420*f*
pneumococcal vaccines 384
Pneumocystis carinii 379
polycystic ovarian syndrome 360
polymyalgia rheumatica (PMR) 418
polysomnography 231
pontine infratentorial hyperintense lesions 29
porencephaly 83
positron emission tomography (PET)
  in giant cell arteritis 422
  in migraine 35, 38
  aura 36
  postdrome 39
  premonitory phase 35
  in visual snow 531–2
post-concussion syndrome (PCS) 314
post-craniotomy headache 434–5
postdromal symptoms, mechanisms 39
post-dural puncture headache (PDPH) 350–1
posterior circulation infarcts 25, 26*f*, 27
postherpetic neuralgia (PHN) 394, 394*b*, 471
post-ictal headache 122, 123*b*
post-lumbar puncture headache 434
post-traumatic headache (PTH) 6, 314–15, 503–4
  clinical features 317
  epidemiology 315–16
  ICDH-3 criteria 315*b*
  management 319
  mechanisms 318
  recent studies 316*t*
  risk factors for 316–17
  sports-related 317–18
  in US soldiers and Veterans 318
precipitating factors 13–14
  see also trigger factors
prednisolone
  in giant cell arteritis 423
  see also steroids
prednisone
  cluster headache prophylaxis 185
  in migraine 146
  in PCNSV 425
  in status migrainosus 145
  see also steroids
pre-eclampsia 376*b*
PREEMPT (Phase 3 REsearch Evaluating Migraine Prophylaxis Therapy) studies 277
pregabalin
  in lacrimal neuralgia 252–3
  in SUNCT and SUNA 199
  in trigeminal neuralgia 241
pregnancy
  effect on migraine 69, 484–5, 486*f*, 490*b*
  idiopathic intracranial hypertension 364
  migraine as risk factor 334
  migraine treatment 488–9
pre-ictal headache 122
PREMICE (PREvention of Migraine using Cefaly) study 170
premonitory symptoms 12, 13*f*, 62
  mechanisms 35–6
primary angiitis of the central nervous system (PACNS) *see* primary central nervous system vasculitis 339
primary central nervous system vasculitis (PCNSV) 424
  clinical features 421*t*, 424–5
  differentiation from RVCS 424*t*, 451
  ICDH-3 criteria 424*b*
  investigations 425
  management 425
primary exercise headache 70, 503*b*, 504
  ICDH-3 criteria 227*b*
  see also exertional headaches
primary headache associated with sexual activity
  ICDH-3 criteria 5, 227*b*
  see also sexual headaches
primary headache disorders 3
  ICDH-3 criteria 4–6
primary stabbing headache (PSH) 215, 392, 393*b*
  clinical features 215–16*b*
  differential diagnosis 216–17
  epidemiology 215
  ICDH-3 criteria 5, 6*b*, 216*b*
  investigations 217
  pathophysiology 217
  prognosis 218
  treatment 217–18
primary thunderclap headache 311–12
  ICDH-3 criteria 5–6*b*
primary trochlear headache 395–6
PRISM (Precision Implantable Stimulator for Migraine) study 169
probable trigeminal autonomic cephalalgia, ICDH-3 criteria 178*b*
procarbazine 434
prochlorperazine 145, 146
progesterone, role in menstrual migraine 484, 487
prolactinoma 433
  see also pituitary tumours
propranolol
  in idiopathic intracranial hypertension 363*t*
  impact on sleep 518*t*, 519
  migraine prevention 153–4
  pregnancy and lactation 489*t*
  see also beta blockers

PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) study
infarct-like lesions 100
white matter lesions 101
prostaglandins, role in migraine headache 38–9, 69, 71
prothrombotic factors, association with migraine 104
protozoal infections 379
provocation trials in migraine 67–8
PRRT2 78
pseudo-SAH 309, 385*f*
pseudotumour cerebri *see* idiopathic intracranial hypertension434
psychiatric comorbidities 475
chronic daily headache 463
epidemiology 476
fibromyalgia 525
historical background 475
ICDH-3 criteria 9
migraine 112*t*, 113, 462–3, 477–8*t*
pathophysiological bases 475–6
prognosis 479
risk factors 476–7
substance dependence and abuse 479
suicide risk 478–9
ptosis
cluster headache 182, 183
hemicrania continua 204
hypnic headache 231
paroxysmal hemicrania 190
pulpitis 239*t*
pupillary dilatation 13
angle closure glaucoma 396

Q fever 379
quality of life 479
children 463–4, 465
in chronic migraine 276, 277, 279, 285
in fibromyalgia 524, 525–6, 527
in idiopathic intracranial hypertension 361
impact of childhood headaches 527
in trigeminal neuralgia 241, 242
Quincke, Heinrich 356

radiofrequency neurotomy 328*f*
radioisotope cisternography 348–9
radiotherapy-induced headache 434
rashes 13
Raynaud's phenomenon
HANAC syndrome 83
RVCL-S 82, 83
rectal sumatriptan 141
recurrent episodes 15
recurrent painful ophthalmoplegic neuropathy (RPON) 393, 394*b*
red ear syndrome 254
red wine 67
relaxation training 263
relieving factors 14
REM sleep behaviour disorder (RBD) 517
restless legs syndrome (RLS), comorbidities 112*t*, 114, 517
retinal artery occlusion 421
retinal migraine 92–3
clinical vignette 93
diagnostic work-up 94*t*
differential diagnosis 94
epidemiology 93–4
ICDH-3 criteria 93*b*
management 95
pathophysiology 93
prevention 94
prognosis and complications 94–5
reversible cerebral vasoconstrictor syndrome (RCVS) 270*f*, 271, 310–11, 447
associated factors 448*b*
case histories 448*f*
clinical features 449
headache characteristics 335*t*, 337
diagnosis 450–1
differentiation from PCNSV 424*t*
epidemiology 447
glucocorticoid-associated deterioration 453*f*
ICDH-3 criteria 6, 7*b*
investigations
blood and serological tests 449
neuroimaging 448*f*, 449–50, 452*f*
management 451–4
mechanism 448–9
sexual headaches 227–8
rheumatoid arthritis (RA) 325
temporomandibular joint 401
rhinitis, chronic 412
rhinorrhoea 197
paroxysmal hemicrania 191
SUNA 198
SUNCT 197, 199
rhinosinusitis 411–12
definitions 411*t*
medical therapies 414*t*
see also sinus headaches
riboflavin, migraine prevention 154*t*, 157, 165–6
rickettsia infections 379
rizatriptan 142, 143*t*
in children 464
in menstrual migraine 487
pharmacokinetics 490*t*
in vestibular migraine 133
Rocky Mountain spotted fever 379
rofecoxib 217
ropivacaine 240*t*, 241
RVCL-S (retinal vasculopathy with cerebral leukodystrophy and systemic manifestations) 81–3, 102*t*, 339
mouse models 85

'sausage on a string' appearance 448*f*, 450
scalp sensitivity 62
Scandinavia, MOH management 288
schizencephaly 83
scintillating scotoma 36
drawings of 54*f*, 55*f*, 56*f*
SCN1A mutations 78, 121
secondary headache disorders 3
ICDH-3 criteria 6–9
general diagnostic criteria 6*b*
in older adults 471
stroke-related 98
seizure-related headaches
classification 122–4, 123*b*
reversible cerebral vasoconstrictor syndrome 449
sensory aura 64
sensory sensitivity
migraine 36
mechanisms 39
paroxysmal hemicrania 191–2
see also phonophobia; photosensitivity
sentinel headache 307, 336–7
serotonergic system, effect of oestradiol 486
serotonin hypothesis 34–5, 38
serotonin syndrome 143
sertraline 363*t*
sexual activity
primary headache associated with sexual activity
ICDH-3 criteria 5
relationship to migraine 70
sexual headaches 221, 312
clinical features 226
diagnosis 226
differential diagnosis 226–7
epidemiology 226
historical background 225
ICDH-3 criteria 227*b*
pathophysiology 227
prognosis 228
reversible cerebral vasoconstrictor syndrome 447–54
treatment 227–8
short-lasting unilateral neuralgiform headaches
classification 197*b*
diagnostic criteria 197*b*
see also SUNA; SUNCT
sildenafil 70
single photon emission computed tomography (SPECT)
in HaNDL 405, 406*f*
in migraine 34–5
sinus headaches
differential diagnosis 414
historical background 409
ICDH-3 criteria 410*b*
management 414*t*–15
McAuliffe and Wolfe's experiments 409, 410*b*
nature of 409
potential mechanisms 414*f*
specific disorders 410–11*t*
acute and chronic rhinosinusitis 411–12
airplane headaches 413
chronic rhinitis 412
infraorbital nerve dehiscence 413
mid-segment facial pain 413
mucosal contact points 413
vacuum headaches 412–13
sinuses, innervation of 410
SLC1A3 mutations 84, 121
sleep, trigger factors for migraine 69–70
sleep anatomy 514
link between headache and sleep 514–15*t*
sleep apnoea headache 373*b*–4
sleep deprivation 260
sleep disorders 514
association with headache disorders 517–18
association with idiopathic intracranial hypertension 360
exploding head syndrome 251
fibromyalgia 525
headache as a cause 516*t*–17
headache as a symptom 517
headache medication as a cause 518–19
migraine comorbidity 112*t*, 113–14
in older adults 471
sleep medication, as cause of headache 519
Sluder's neuralgia 409
smoking
cardiovascular disease risk 105
as a migraine trigger 70
Sneddon syndrome 340
sodium valproate
in hemicrania continua 205
in idiopathic intracranial hypertension 363*t*
impact on sleep 518
in migraine 146, 155–6
in older adults 473
somatosensory-evoked responses, changes in migraine 34
Spain, MOH management 288–9
speech disturbance 64
sphenopalatine ganglion (SPG) blocks 186
sphenopalatine ganglion stimulation 169
spinal cord injury (SCI) 376*b*
spinal trigeminal nucleus (STN) 358
spinocerebellar ataxia type 6 (SCA6) 84–5
spontaneous intracranial hypotension (SIH) 270*f*, 271, 311, 346
clinical features 347–8
complications 352
epidemiology 346
ICDH-3 criteria 347*b*
investigations
lumbar puncture 348
neuroimaging 348–50
screening for other disorders 351–2
SEEPS mnemonic 349*b*
pathophysiology 346–7
prognosis 352
treatment 350–1
sporadic hemiplegic migraine (SHM) 75, 78*b*
see also hemiplegic migraine
sporting activity
coincidental primary headache syndromes 503–4
medication in elite sportspeople 504
migraine 504
see also exertional headaches
sports-related post-traumatic headache 317–18
spreading depolarizations (SDs), and recovery after stroke 340
spreading depression, retinal 93
see also cortical spreading depression (CSD)
stabbing headaches 216–17
status migrainosus 146–7
stenting, dural venous sinuses 362–3
steroids
in bacterial meningitis 386
in giant cell arteritis 422, 423
in headache secondary to intracranial neoplasia 430
in hemicrania continua 205
impact on sleep 518*t*, 519
in migraine 145, 146
in PCNSV 425

in RVCS, clinical worsening 453*f*
in spontaneous intracranial hypotension 350
in SUNCT and SUNA 199
stomatodynia (burning mouth syndrome) 244–5
stress, as a trigger factor 68*f*–9, 268
stroke
headache as a prognostic factor 339–40
pathophysiology 341
headache as a symptom 334–6
pathophysiology 341
stabbing headache 216
MELAS 84
and migraine 18–19, 31, 98
clinical ischaemic stroke 22–3, 25
haemorrhagic stroke 25
pathophysiology 340–1
subclinical stroke 25, 26*f*, 27
migrainous infarction 19–22, 98
reversible cerebral vasoconstrictor syndrome 449–50, 451
secondary headache 98
subclinical 25, 26*f*, 27, 30
thunderclap headache 311
Stroke in Young Fabry Patients (SIFAP1) study 335
stroke risk, migraine 99–100*b*, 101*t*, 334
mechanisms 103–5, 104*f*
risk management 105
Strongyloides stercoralis 379
subacute onset 15–16
subarachnoid haemorrhage (SAH)
clinical features 307
headache 335*t*, 336–7
diagnosis
aneurysm detection 309–10
CSF analysis 309
CT 307–9
CT mimics 309
epidemiology 307
prognosis 310
reversible cerebral vasoconstrictor syndrome 450, 452*f*
treatment 310
subcutaneous sumatriptan 141
subdural empyema 389
subdural haematoma 471
association with CSF leaks 352
suboccipital muscle stimulation, pattern of referred pain 323
substance abuse 8, 479
sudden onset 15–16
neuroimaging 17
see also thunderclap headache
'suicide headache' *see* cluster headache
suicide risk 478–9
fibromyalgia 526
sumatriptan 141–2, 143*t*, 146
association with MOH 287
in cluster headache 185
combination with NSAIDs 143
in migraine
international comparisons 287
in paroxysmal hemicrania 193
pharmacokinetics 490*t*
pregnancy and lactation 489*t*
in status migrainosus 146
see also triptans
SUNA (short-lasting unilateral neuralgiform headache attacks with cranial autonomic features) 196
association with pituitary tumours 432–4, 436*t*
clinical features 179*t*, 198
diagnosis
ICDH-3 criteria 178*b*, 198*b*
differential diagnosis 180
trigeminal neuralgia 239*t*
epidemiology 178–9
nosology 200
in older adults 471
pathophysiology 198–9
primary and secondary forms 198
treatment 180, 199
SUNCT (short-lasting unilateral neuralgifom headache attacks with conjunctival injection, tearing, sweating, and rhinorrhoea) 196
association with pituitary tumours 432–4, 436*t*
clinical features 179*t*, 196–8
temporal profile 197*f*
diagnosis
ICDH-3 criteria 178*b*
differential diagnosis 180
paroxysmal hemicrania 192, 193*t*
trigeminal neuralgia 199, 200*f*, 239*t*
epidemiology 178–9
ICDH-3 criteria 197*b*
nosology 199–200
in older adults 471
pathophysiology 198–9
post-traumatic 317
primary and secondary forms 198
SUNCT tic syndrome 209–10*b*
treatment 180, 199
sunlight exposure, effect on migraine 496
suprachiasmatic nucleus 183
supraorbital nerve block 199
supraorbital nerve stimulation 169–70
Sydenham, Thomas 47
syncope, migraine comorbidity 113*t*
systemic infection-associated headaches 378–9
aetiology 379
epidemiology 379
ICDH-3 criteria 378*b*
management 380
pathophysiology 379–80

Taiwan, headache management 285
T-cells, role in GCA 419, 420*f*
telcagepant 147
temozolomide 434
temperature, effect on migraine 495–6
temporal artery
halo sign 422
swelling 422*f*
temporal artery biopsy 422
temporal patterns of headache 12, 13*f*
cluster headache 182
hemicrania continua 203
migraine 61
nummular headache 298–9
paroxysmal hemicrania 191
primary stabbing headache 215–16
SUNCT 196–7*f*
temporomandibular joint (TMJ) 401
temporomandibular joint disorders 400–2
clinical features 239*t*
ICDH-3 criteria 9*b*
tension-type headache (TTH) 13, 444*t*, 503
central sensitization 525
clinical features 259
comorbidities
fibromyalgia 523–4*t*
psychiatric 476, 477
sleep disturbance 516
diagnosis 259–60
epidemiology 259
ICDH-3 criteria 9, 260*b*
in older adults 471
pathophysiology 260
patient education 263
post-traumatic 317
subtypes 259, 260*b*
temporal pattern 13*f*
treatment
acute drug therapy 260–1*t*
non-pharmacological 263–4
prophylactic 262*t*–3
twentieth century theories 55–6
weather-related effects 494
thalamus
pain functions 515*t*
role in migraine headache 37
role in sensory sensitivity 39
The Health Improvement Network (THIN) 99
thioctic acid 166
third occipital headache 326
third occipital nerve blocks 326*f*
diagnostic use 327
Thomas, Louis Hyacinthe 54
thunderclap headache 13*f*, 15, 307
causes 308*b*, 311
cerebral venous sinus thrombosis 311
cervical artery dissection 311
colloid cyst of the third ventricle 431–2
diagnostic evaluation 308*f*, 449, 451
pituitary apoplexy 311, 432
primary 311–12
ICDH-3 criteria 5–6*b*
reversible cerebral vasoconstrictor syndrome 6, 271, 310–11, 447–54
spontaneous intracranial hypotension 311, 347
stroke 311
subarachnoid haemorrhage 307–10, 336–7
thyroid eye disease (TED) 397
tic douloureux *see* trigeminal neuralgia
time of onset 12
timolol 363*t*
see also beta blockers
tinnitus
carotid artery dissection 395
idiopathic intracranial hypertension 358
Tissot, Samuel 48–9
tizanidine 262
t*MT-TL1* mutations 84
tocilizumab 423–4
Toll-like receptors (TLRs), role in GCA 419
tooth pains 399–400
topiramate
as cause of Alice in Wonderland syndrome 249
in cluster headache 185
in hemicrania continua 205
in hypnic headache 234
in idiopathic intracranial hypertension 362, 363*t*
impact on sleep 518
in migraine 154*t*, 156, 158, 279, 280
retinal 93
vestibular 133
in nummular headache 301
in paroxysmal hemicrania 193
in SUNCT and SUNA 199
in tension-type headache 262
toxic headaches 367, 368*b*
alcohol-induced 369
calcitonin gene-related peptide-induced 370
carbon monoxide-induced 369
cocaine-induced 369–70
drugs implicated 367–8
epidemiology 367
exogenous acute pressor agent-induced 370
histamine-induced 370
ICDH-3 categorization 368*b*
ICDH-3 criteria 368*b*
management 371
miscellaneous causes 370–1
nitric oxide donor-induced 368
non-headache medication-induced 370
in older adults 472
pathophysiology 368
phosphodiesterase inhibitor-induced 369
Toxoplasma gondii 379
tramadol 145, 146
transcranial direct current stimulation (tDCS) 170–1
transcranial magnetic stimulation (TMS)
in fibromyalgia 526
in migraine 147, 160–1, 170
transcutaneous electrical nerve stimulation (TENS) 169
in cervicogenic headache 327
in nummular headache 301
transcutaneous supra-orbital nerve stimulation 160
transdermal sumatriptan 141
transformed migraine (TM) 275, 476–7
diagnostic criteria 277*b*
temporal pattern 13*f*
transient ischaemic attack (TIA)
differentiation from aura 98
headache as a prognostic factor 339–40
headache as a symptom 335
migraine as risk factor 99, 100*b*
transient obscurations of vision (TOV) 358
transverse sinus stenosis 360*f*
trauma-associated headache
ICDH-3 criteria 6
see also post-traumatic headache
traumatic brain injury (TBI) 314
post-concussion syndrome 314
see also post-traumatic headache

trazodone, impact on sleep 518*t*, 519
TREX1 mutations 81–3
tricyclic antidepressants
in idiopathic intracranial hypertension 363*t*
impact on sleep 519
in nummular headache 301
in retinal migraine 95
trigeminal autonomic cephalalgias (TACs) 177
association with pituitary tumours 435*t*
epidemiology 432–3
management 433–4
pathophysiology 433
classification 177–8*b*
clinical features 179*t*
differential diagnosis 179–80
differentiation from hypnic headache 233
epidemiology 178–9
in older adults 471
pathophysiology 180
primary or secondary nature 178
treatment 180
see also cluster headache; hemicrania continua; paroxysmal hemicrania; SUNA; SUNCT
trigeminal autonomic reflex 180*f*, 183, 184*f*, 204
trigeminal ganglion interventions 241–2
trigeminal nerve
clinical features of neuropathy 244
neuroanatomical basis of cervicogenic headache 322
role in migraine headache 37
surgical procedures 199
see also painful post-traumatic trigeminal neuropathy
trigeminal neuralgia (TN) 393, 394*b*, 471
classification 237
ICDH-3 criteria 9*b*–10, 238*b*
clinical features 237–8
cluster tic syndrome 208–9*b*
diagnosis 239–40
differential diagnosis 180, 239*t*
dental pathology 400
paroxysmal hemicrania 192
SUNCT 199, 200*f*
epidemiology 237
investigations 240
paroxysmal hemicrania tic syndrome 209–10*b*
pathophysiology 237
secondary 239, 436–7
sleep disturbance 517
SUNCT tic syndrome 209–10*b*
treatment 241*f*, 394
medical 240*t*–1
surgical procedures 241–2
trigeminovascular system 341
trigger factors 13–14, 67, 68*t*, 138
atmospheric 67
clinical implications 71–2
cluster headache 182
cough headache 221
electromagnetism 498
female hormones 69
food 67–8
hemicrania continua 203
hemiplegic migraine 79
lifestyle factors 69–70
new daily persistent headache 267–8
nummular headache 298
paroxysmal hemicrania 192
patient perceptions 71
pharmacological 70–1
primary stabbing headache 216
psychosocial stress 68*f*–9
reversible cerebral vasoconstrictor syndrome 310
SUNCT 196
tension-type headache 263
trigeminal neuralgia 238
vestibular migraine 133
weather-related 494–6
trigger points 401
trimipramine, impact on sleep 518*t*
triptans 38, 140*t*, 141
adverse effects 143
in airplane headache 511–12
almotriptan 142
association with MOH 287
in children 464
choice of drug 143*t*
combination with NSAIDs 143
contraindications 142, 143
in cyclic vomiting syndrome 461
eletriptan 142
frovatriptan 142
in migraine 488
abdominal migraine 461
in hemiplegic migraine 79–80
international comparisons 287
menstrual migraine 487–8
status migrainosus 146
vestibular migraine 133
naratriptan 142
in older adults 473
pharmacokinetics 490*t*
pregnancy and lactation 489*t*
rizatriptan 142
in sexual headache 228
and sport 503
and stroke risk 103
sumatriptan 141–2
in tension-type headache 261
therapeutic targets of 130
zolmitriptan 142
trochleitis 394*b*, 395–6
trypanosomiasis 379
tuberculous meningitis 389
tumour necrosis factor (TNF)-α
role in NDPH 268
role in post-traumatic headache 318
tumours
orbital 397–8
see also intracranial neoplasms
tyramine 67

ubiquinone *see* coenzyme Q10
ubrogepant 147
United States, headache management 285
unruptured aneurysms 338

vacuum headaches 412–13
vagoglossopharyngeal neuralgia *see* glossopharyngeal neuralgia
vagus nerve stimulation (VNS) 169, 170
in cluster headache 186, 289
in migraine 147
in paroxysmal hemicrania 193
valproic acid *see* sodium valproate
Valsalva manoeuvres 347
airplane headache 511
Chiari malformation type I 7, 8*b*, 442, 445*b*
cough headache 220–1, 503*b*, 504
exertional headaches 225, 226
infection-related headaches 378, 388*b*
reversible cerebral vasoconstriction syndrome 7*b*, 310, 451
tumour-related headaches 430, 431*b*
vascular disease
migraine as risk factor 100*b*, 101*t*
see also myocardial infarction; stroke risk
vasculature, effects of oestradiol 486–7
vasculitis *see* giant cell arteritis; primary central nervous system vasculitis
vasoactive intestinal peptide (VIP), role in TACs
cluster headache 183
paroxysmal hemicrania 190
vasogenic oedema 452*f*
venlafaxine
migraine prevention 154*t*, 155
in tension-type headache 262*t*
venous distension sign, SIH 349
venous hinge sign, SIH 349
venous pressure, raised 503
venous thromboembolism, association with migraine 340
ventriculoatrial shunts 363–4
ventriculojugular shunts 363–4
ventriculoperitoneal shunts (VPS) 363–4
verapamil
in cluster headache 185
in hemiplegic migraine 80
in idiopathic intracranial hypertension 363*t*
in SUNCT and SUNA 199
vertebral artery pathology 326–7
vertigo 64
benign paroxysmal positional vertigo 129, 131
definition 128
differential diagnosis 132–3
migraine comorbidity 128
see also vestibular migraine
prevalence 129
veisalgia cephalgia 369
vestibular evoked myogenic potentials (VEMP) 132
vestibular migraine 128
clinical examination 131
clinical features 130–1
diagnostic cautions 132–3
diagnostic work-up 131–2
epidemiology 128
genetic factors 129–30
ICDH-3 criteria 4, 129*b*
management 133
natural history 129
neurochemical links 130
rehabilitation 134
related disorders 131
vestibular vertigo 129
viral encephalitis 388*b*
viral infections, as trigger for NDPH 268
viral meningitis 387*b*–8
diagnostic criteria 388*b*
visual aura 36, 53*f*, 54*f*, 55*f*, 56*f*, 62, 63*f*
visual field abnormalities 359*f*
visual impairment
differential diagnosis 94
giant cell arteritis 421
in idiopathic intracranial hypertension 358
retinal migraine 92–5
reversible cerebral vasoconstrictor syndrome 449
spontaneous intracranial hypotension 348
visual snow
associated symptoms 530
clinical features 530, 531*f*
diagnosis 532
ICDH-3 criteria 532*b*
investigations 532
management 532–3*t*
pathophysiology 531–2
relationship to hallucinogenic drugs 530–1
relationship to migraine 531

warning leaks, aSAH 307, 336–7
watershed infarcts, reversible cerebral vasoconstrictor syndrome 452*f*
weather-related effects 67, 494–6
clinical studies, difficulties with 498–500
weight loss, effect on idiopathic intracranial hypertension 361
Wepfer, Johann Jakob 47
West Nile virus 379
whiplash, third occipital headache 326
white matter lesions (WMLs) 18–19, 28*f*, 29*f*, 100–1, 101*t*, 102*f*, 103*f*
CAMERA studies 27
clinical significance 30
EVA, ARIC, and NOMAS studies 28
pathophysiological mechanisms 28–9
Willis, Thomas 47, 48*f*
Wolff, Harold 52, 54–5
Women's Health Study 116, 334, 490

Yom Kippur headache 377

zolmitriptan 142, 143*t*
in cluster headache 185
in migraine 488
vestibular 133
pharmacokinetics 490*t*
zonisamide, in SUNCT and SUNA 199
zygapophyseal joints
referred pain 323, 326
therapeutic interventions 328